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THE CALORIGENIC ACTION OF THYROID AND SOME OF ITS ACTIVE CONSTITUENTS*

J. LERMAN, M.D. AND W. T. SALTER, M.D.

From the Metabolism Laboratory and Thyroid Clinic of the Massachusetts General Hospital and the Biochemical Research Department of the Huntington Memorial Hospital

BOSTON

One of the outstanding advances in the study of the thyroid during the past two decades has been the recognition of definite organic iodine-containing compounds in the gland, and their chemical isolation. The possibility of a dual hormone has been considered before but this chemical progress for the first time has offered a definite basis for testing this hypothesis. The far-reaching importance of such a condition is apparent from both clinical and pathological viewpoints. It follows that a clear understanding of the metabolic effect of all the organic iodine compounds is essential. Only through this information can one appreciate the true nature of the thyroid hormone and its variations in nature and in disease.

In the past few years we have been engaged in the assay of the thyroid hormone and some of its constituents. Our chief aim has been to investigate problems in thyroid physiology with reference to the metabolic activity of various organic iodine compounds in the gland. In connection with this work we have also determined the calorigenic activity of some commercial preparations of thyroid.

When Harington and Salter (1) obtained thyroxin in peptide combination by subjecting thyroid to proteolytic hydrolysis, they concluded that this is the form in which thyroxin actually exists in the gland. They further stated that this peptide compound alone is responsible for the physiologic action of whole thyroid gland. They inferred that the differences in action of whole thyroid and crystalline thyroxin depend solely on differences in the physical properties of thyroxin and thyroxin polypeptide, that is to say, their solubilities, optical activities, and availabilities to the body by different routes of entry. To establish such hypotheses it would be necessary to compare the calorigenic action of thyroxin, thyroxin polypeptide and whole thyroid gland.

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Direct comparison between thyroxin and whole thyroid is impossible because the latter can safely be given only via the gastro-intestinal tract whereas the former exerts an uncertain action when given by this route. Thyroxin and thyroxin polypeptide can be compared because both may be given by the parenteral route. Moreover, since thyroxin polypeptide is more soluble than thyroxin it was expected that the polypeptide would be absorbed sufficiently well when given by mouth to make comparison with whole thyroid possible. Thus thyroxin and whole thyroid, though not comparable directly, could each be compared with the polypeptide.

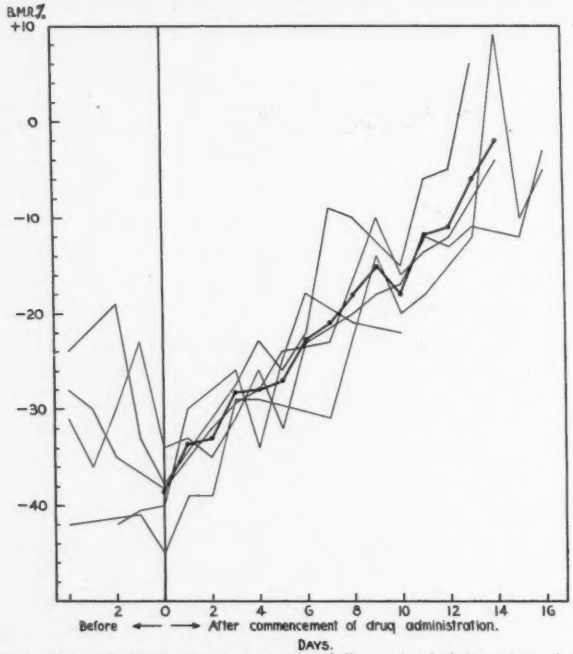

Figure 1. The calorigenic response to the daily oral administration of 1.0 mg. of thyroxin polypeptide (containing 0.49 mg. of iodine) in five cases of myxedema. The heavy line represents the composite of the individual responses.

The assays were carried out in patients with complete untreated myxedema, who were kept in the hospital during the test. Daily metabolic rates were determined in each case prior to the administration of any thyroid preparation, until a level had been established. The determinations were repeated daily after the drug had been given until it was thought the maximum response had been obtained. No patient was used for more than one assay.

The first series of observations was on five patients with myxedema who received daily oral rations of 1 mg. of thyroxin polypeptide. The results of the individual responses are shown graphically in Figure 1, as well as the composite of the five. The curves indicate a pronounced meta-

bolic response of a definite order of magnitude, namely, about 2.5 points per day.

The next series of observations was on four patients with myxedema who received daily 1 mg. rations of polypeptide, this time given intravenously. The results, as shown in Figure 2, are somewhat more irregular than the previous group, but indicate a definite calorigenic response, similar in degree to that of the oral group. The slope of the composite curve is approximately 2.7 points per day.

To confirm the above observations another method of assay was used, namely, the comparison of the effect of a single large dose when given by

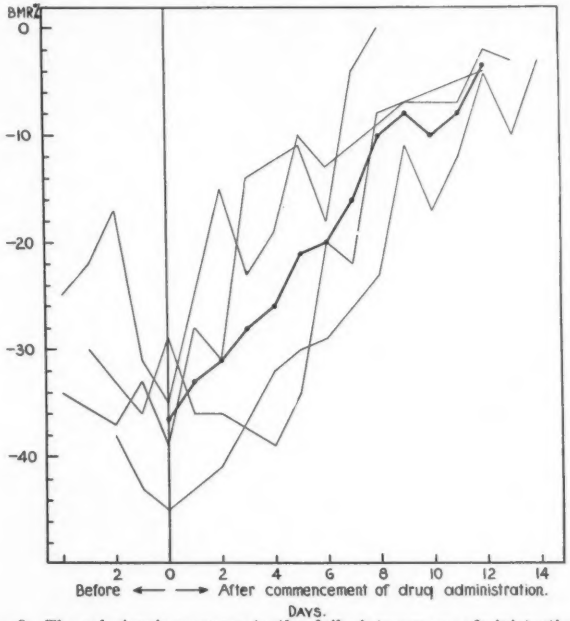

Figure 2. The calorigenic response to the daily intravenous administration of 1.0 mg. of thyroxin polypeptide (containing 0.49 mg. of iodine) in four cases of myxedema. The heavy line represents the composite of the individual responses.

the oral route with that by the intravenous route. One patient with myxedema received 13 mg. of thyroxin polypeptide in a single dose by mouth and another received 13 mg. intravenously. The resulting metabolic changes are illustrated in Figure 3. The response to intravenous administration was slightly greater than that to oral administration, but not to a degree that is significant. The intravenous curve reaches its maximum on the sixth day at a rate of 7.0 points per day, whereas the oral curve reaches its maximum, also on the sixth day, at a rate of 5.2 points per day.

In Figure 4 the curve of response to the single intravenous dose of 13 mg. of thyroxin polypeptide is compared to two curves obtained in this clinic by Thompson, et al. (2), showing the response of myxedema patients

to a single injection of 10 mg. of crystalline thyroxin. This dose of thyroxin has the same iodine content as 13 mg. of polypeptide. It can be seen from the graph that there are no significant differences among the three curves. In fact, the polypeptide curve for the most part lies between the two thyroxin curves.

Having demonstrated that thyroxin polypeptide has calorigenic activity when given orally almost to the same degree as when given intravenously and that its action is equal to that of pure thyroxin when the two are given in dosages containing equal amounts of iodine, we then determined the calorigenic response of whole thyroid gland. The composite curve of

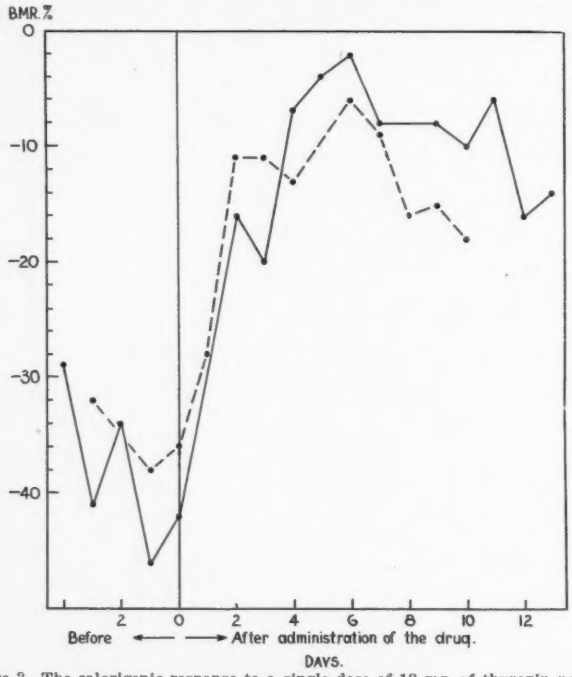

Figure 3. The calorigenic response to a single dose of 13 mg. of thyroxin polypeptide (containing 6.5 mg. of iodine) in two cases of myxedema. The intravenous route is shown by the solid line and the oral route by the interrupted line.

Figure 1 was adopted as a standard for comparison. Since it is known that the organic iodine of whole thyroid gland exists partly in the form of thyroxin and partly in the form of diiodotyrosin (3), the various thyroid preparations used in these, as well as in other assays, were analyzed for total organic iodine and thyroxin iodine* according to the method of Harington and Randall (4).

*In selecting our analytical method we were forced to choose between the procedure of Harington and Randall and that of Leland and Foster (5). The latter method gives lower values for thyroxin content. In view of the comparative newness of both procedures, it seemed to us expedient to use a method which gives higher results. In consquence there is a tendency to credit thyroid substance with a maximum amount of thyroxin and thus to strengthen the basis of our main thesis.

It should be noted that inorganic iodine is assumed to be negligible in these studies. Consequently the term "total organic iodine" has been used as synonymous with "total iodine." The result is a tendency to credit thyroid substance with a maximum amount of organic iodine.

Three patients with untreated spontaneous myxedema were given daily 15 grains (1.0 Gm.) of a lot of Armour & Company's thyroid, which had been found by analysis to contain 0.05 per cent of thyroxin or so-called "active" iodine (the acid insoluble fraction) and 0.22 per cent of total organic iodine. This dose of thyroid contains 0.49 mg. of thyroxin iodine

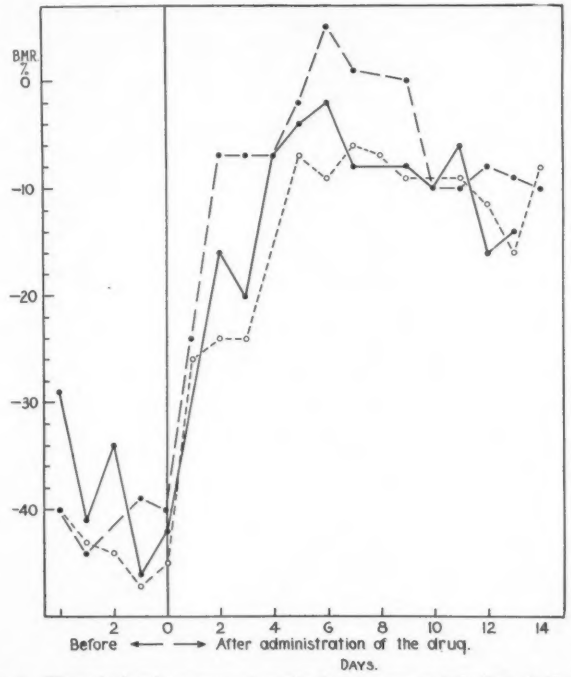

Figure 4. The calorigenic response to a single intravenous injection of 13 mg. of thyroxin polypeptide (containing 6.5 mg. of iodine) in a case of myxedema, shown by the solid line; and that to a single intravenous injection of 10 mg. of crystalline thyroxin (also containing 6.5 mg. of iodine) in two cases of myxedema, shown by the interrupted lines.

and 2.2 mg. of total organic iodine. The amount of thyroxin iodine is the same as in 1 mg. of thyroxin polypeptide used in obtaining the data for Figure 1. The results are shown in Figure 5 (upper three curves), together with the composite curve from Figure 1 (heavy solid line).

If now the calorigenic action of whole thyroid depends upon its thyroxin iodine and not upon its total organic iodine content, then the curves of the assays with 15 grains of Armour's thyroid should have slopes similar to those of the polypeptide assays. However, it is clear from Figure 5 that all three curves are distinctly steeper than the composite polypeptide curve.

We have also made assays with whole gland preparations containing much less thyroxin iodine than does 1 mg. of thyroxin polypeptide. Three patients with spontaneous myxedema received daily 5.3 grains (0.35 Gm.) of Armour & Company's thyroid orally, which was found by analysis to contain 0.16 mg. thyroxin iodine and 0.69 mg. of total organic iodine. The composite of the three assays is shown in Figure 6 (light solid line and solid circles). Another patient, suffering from untreated cachexia strumipriva, received a daily oral dose of 15 grains (1.0 Gm.) of Burroughs Wellcome & Company's fresh gland preparation of thyroid which was found by

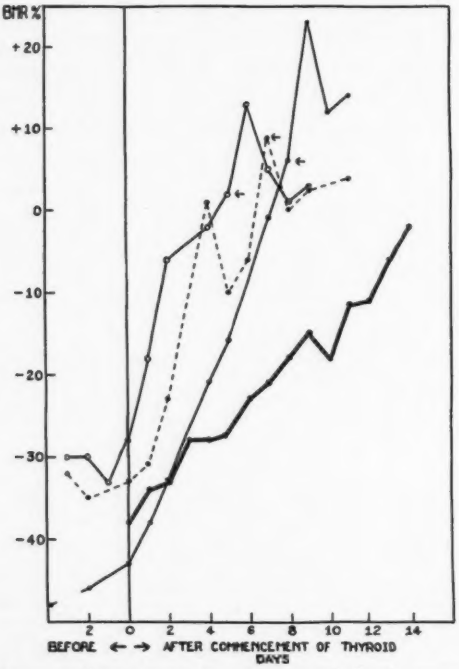

Figure 5. The upper three curves represent the calorigenic responses in three patients with spontaneous myxedema who received daily oral doses of thyroid gland containing 0.49 mg. of thyroxin iodine and 2.2 mg. of total organic iodine. The heavy solid line is the composite from Figure 1, representing 0.49 mg. of thyroxin iodine. The small arrows indicate cessation of medication.

analysis to contain 0.13 mg. of thyroxin iodine and 0.77 mg. of total organic iodine. The calorigenic response is also shown in Figure 6 (interrupted line).

In addition, it seems desirable to include results found in the earlier data of the Thyroid Clinic. Observations on five patients with myxedema are available. They received a daily oral dose of 3 grains (0.2 Gm.) of our stock Armour & Company's thyroid preparation. The total organic iodine was about 0.42 mg. per dose given; the thyroxin iodine was not determined,

but was not more than 0.1 mg. A composite curve of these five responses is also shown in Figure 6 (light solid line and rings).

The importance of the assays of whole thyroid gland charted in Figure 6 is that the thyroxin-iodine fraction in these assays was about one-third or less of what it was in the polypeptide controls. Yet the calorigenic response was close to that obtained by polypeptide. Two of these curves represent the assays of 5.3 grains of Armour's thyroid and 15 grains of Burroughs Wellcome thyroid, with a total organic iodine content per dose of 0.69 mg. and 0.77 mg., respectively. They are as steep as or steeper than

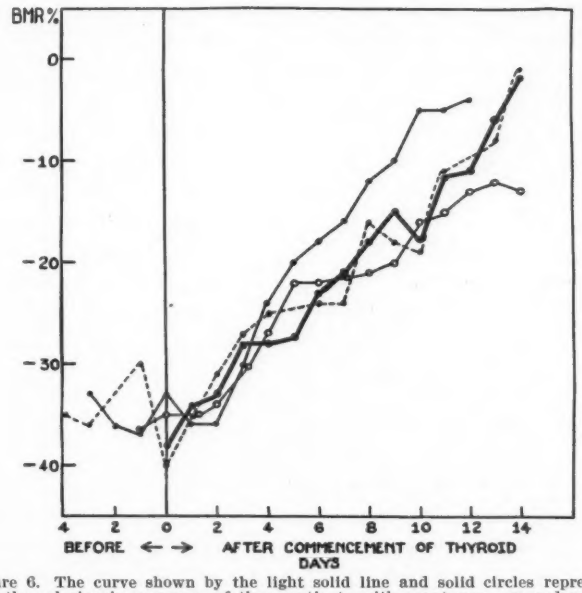

Figure 6. The curve shown by the light solid line and solid circles represents the composite of the calorigenic responses of three patients with spontaneous myxedema who received daily oral doses of thyroid gland containing 0.16 mg. of thyroxin iodine and 0.69 mg. of total organic iodine. The curve shown by the interrupted line is the response of a patient with cachexia strumipriva who received a daily oral dose of thyroid gland containing 0.13 mg. of thyroxin iodine and 0.77 mg. of total organic iodine. The curve shown by the light solid line and rings is the composite of the calorigenic responses of five patients with spontaneous myxedema who received daily oral doses of thyroid gland containing 0.42 mg. of total organic iodine. The heavy solid line is the composite from Figure 1, representing 0.49 mg. of thyroxin iodine.

the polypeptide control curve, probably by virtue of the higher total organic iodine. The average slope of these two curves is 2.9 points per day. On the other hand, the composite curve of the assays of 3 grains of Armour's thyroid, with an average slope of 2.0 points per day, is slightly less steep than the polypeptide curve. The total organic iodine in these assays was nearly that contained in thyroxin polypeptide dosage, i.e., 0.42 mg. versus 0.49 mg.

It seems clear, therefore, that thyroxin iodine alone does not represent the entire calorigenic activity of whole thyroid, but that total organic iodine

does. Additional proof of this has been obtained in other studies to be presented below and the work of Thompson, et al. (6), also supplies proof of a similar nature. Thus we are led to a paradox. The acid-soluble iodine fraction of iodothyroglobulin, which is diiodotyrosin, has been shown by Thompson and Alper (7) and others (8) to be inert when given alone to patients with myxedema. Yet it exerts calorigenic action when given in its natural chemical combination with thyroxin in the form of whole gland.

The next step in the investigation was to determine at what stage diiodotyrosin becomes inactive in its isolation from whole gland. For this part of the work thyroglobulin was prepared from human glands, removed at operation, according to the method employed by Harington and Salter (1) for sheep thyroid. Essentially the process consists of extracting the ground-up glands with 0.02N NaOH and precipitating the thyroglobulin from the extract at its isoelectric point (pH = 5.0) by the addition of 0.01 N HCl. Some of the thyroglobulin was obtained from glands of patients with hyperthyroidism and some from glands of "non-toxic" patients. Each type was analyzed for total iodine and thyroxin iodine, and assayed separately.

One patient with cachexia strumipriva received a daily ration of thyroglobulin derived from "toxic" glands containing 0.49 mg. of total iodine, an amount equal to that contained in 1 mg. of thyroxin polypeptide. The thyroxin iodine in this dose of thyroglobulin amounted to 0.12 mg.* Two other patients with spontaneous myxedema received a daily ration of thyroglobulin derived from "non-toxic colloid" glands, each dose containing 0.49 mg. total iodine and 0.17 mg. thyroxin iodine. The calorigenic responses are represented graphically in Figure 7. The light solid line and rings represent the response to thyroglobulin from "toxic" glands and the light solid lines and solid circles represent the response to thyroglobulin from "colloid" glands. Here again the curves are no less steep than the polypeptide control (heavy solid line) in spite of the fact that the amount of thyroxin iodine represented by them is much less than that represented by the polypeptide curve. Consequently no calorigenic activity is lost in the extraction of thyroglobulin from whole gland. It may be mentioned in passing that the slope of the curve of assay of thyroglobulin derived from "toxic" glands is steeper than the slope of the polypeptide curve, namely, about 4.9 points per day.

The next procedure was to digest thyroglobulin with pepsin and hydrochloric acid for 72 hours. The method used will be described in another paper and is a modification of the one given by Harington and Salter (1). The products obtained consist chiefly of a soluble diiodotyrosin peptone and an insoluble thyroxin peptone. One patient with myxedema received a daily dose by mouth of diiodotyrosin peptone containing 0.49 mg. of iodine per dose. After nine days of treatment the metabolic rate showed no sig-

*This value was obtained according to the method of Harington and Randall (4). A control analysis by Leland and Foster's method (5) gave 0.10 mg.

nificant change. Thyroxin peptone was therefore substituted in a dose of 0.49 mg. of iodine daily. The resulting calorigenic response is shown in Figure 7 (interrupted line). Both peptones were made from thyroglobulin derived from "toxic" glands. Another patient received diiodotyrosin peptone made from the thyroglobulin derived from "non-toxic colloid" glands in a daily dosage of 0.49 mg. of iodine without any metabolic response. The corresponding thyroxin peptone has caused a metabolic response similar to thyroxin polypeptide but the data are not completed for charting.

It is evident, therefore, that thyroxin peptone has calorigenic action of the same order as thyroxin polypeptide in terms of iodine content and

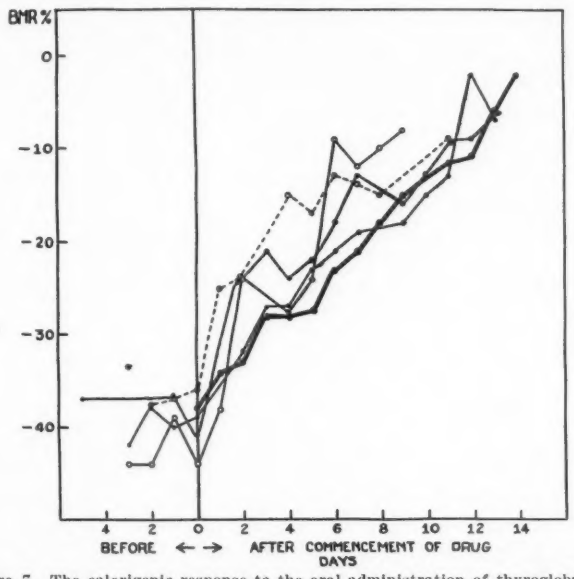

Figure 7. The calorigenic response to the oral administration of thyroglobulin and of thyroxin peptone. One patient with cachexia strumipriva, shown by the light solid line and circles, received daily thyroglobulin derived from "toxic glands" (containing 0.12 mg. of thyroxin iodine and 0.49 mg. of total organic iodine). Two patients with spontaneous myxedema, shown by the light solid lines and solid circles, received daily thyroglobulin derived from "non-toxic" colloid glands" (containing 0.17 mg. of thyroxine iodine and 0.49 mg. of total organic iodine). One patient with spontaneous myxedema, shown by the dotted line, received, daily, thyroxin peptone derived from "toxic glands" (containing 0.49 mg. of thyroxin iodine). The heavy solid line is the composite from Figure 1, representing 0.49 mg. of thyroxin iodine.

that the diiodotyrosin fraction of the total organic iodine of thyroid is inactivated in the first stage of proteolytic digestion of thyroglobulin.

We have, in addition, used another method of clinical assay of thyroid preparations. This consists in determining the maintenance levels of metabolism of a given patient on different preparations. Six lots of thyroid gland tablets were obtained from commercial firms and analyzed according to the method of Harington and Randall (4) for total organic iodine and thyroxin iodine. Twenty patients with treated myxedema were used in this study. Each lot was fed to a patient for a variable period of time, usually

2-3 months, and the maintenance metabolic level obtained by determining the basal rate every 7-14 days. When the metabolism had reached a level, another preparation was substituted. Thus, two or more preparations were

TABLE I

COMPARISON OF THE RELATIVE CALORIGENIC ACTIVITY OF ALL POSSIBLE COMBINATIONS OF COMMERCIAL THYROID PREPARATIONS TESTED

	Ratio of Total Organic Iodine	Ratio of Thyroxin Iodine	No. in Favor of Total Organic Iodine	No. in Favor of Thyroxin Iodine	No. in Favor of Either
1 Armour vs. Lederle	0.22 / 0.28	0.055 / 0.082	—	—	7
2 Armour vs. Burroughs, Wellcome, 1st	0.22 / 0.24	0.055 / 0.050	6	9	2
3 Armour vs. Parke, Davis, 1st	0.22 / 0.20	0.055 / 0.083	12	3	1
4 Armour vs. Burroughs, Wellcome, 2nd	0.22 / 0.26	0.055 / 0.042	5	7	—
5 Armour vs. Parke, Davis, 2nd	0.22 / 0.12	0.055 / 0.047	8	—	1
6 Lederle vs. Burroughs, Wellcome, 1st	0.28 / 0.24	0.082 / 0.050	—	1	5
7 Lederle vs. Parke, Davis, 1st	0.28 / 0.20	0.082 / 0.083	7	—	—
8 Lederle vs. Burroughs, Wellcome, 2nd	0.28 / 0.26	0.082 / 0.042	—	3	—
9 Lederle vs. Parke, Davis, 2nd	0.28 / 0.12	0.082 / 0.047	—	—	3
10 Burroughs, Wellcome, 1st, vs. Parke, Davis, 1st	0.24 / 0.20	0.050 / 0.083	8	2	3
11 Burroughs, Wellcome, 1st, vs. Burroughs, Wellcome, 2nd	0.24 / 0.26	0.050 / 0.042	2	6	1
12 Burroughs, Wellcome, 1st, vs. Parke, Davis, 2nd	0.24 / 0.12	0.050 / 0.047	6	—	1
13 Parke, Davis, 1st, vs. Burroughs, Wellcome, 2nd	0.20 / 0.26	0.083 / 0.042	7	1	3
14 Parke, Davis, 1st, vs. Parke, Davis, 2nd	0.20 / 0.12	0.083 / 0.047	—	—	8
15 Burroughs, Wellcome, 2nd, vs. Parke, Davis, 2nd	0.26 / 0.12	0.042 / 0.047	8	1	—
Total advantage			69	33	35

tested on each patient. In some instances the same patient was fed one thyroid preparation more than once either in the same or in different dosage. The dose of thyroid chosen was the one that from experience was expected

to maintain metabolism within the range of normal standards and keep the patient free from symptoms.

The results of these studies, which will be reported in more detail in another paper, are summarized in Table 1. A series of comparisons between pairs of various preparations is listed, and opposite each pair is given, in the first column, the ratio of their respective total organic iodine, and in the second column, the ratio of their respective thyroxin iodine contents. In each case the metabolic responses were inspected in order to see which analytical value more closely indicated the calorigenic effect. The results are tallied in three separate columns which indicate, respectively, the advantage of total organic iodine, of thyroxin iodine, or of neither. The summated score favors total organic iodine—69 against 33 for thyroxin iodine.

It is interesting that in some comparisons either total organic or thyroxin iodine might be used in expressing the relative calorigenic potency, mainly because the respective ratios between the total organic iodine con-

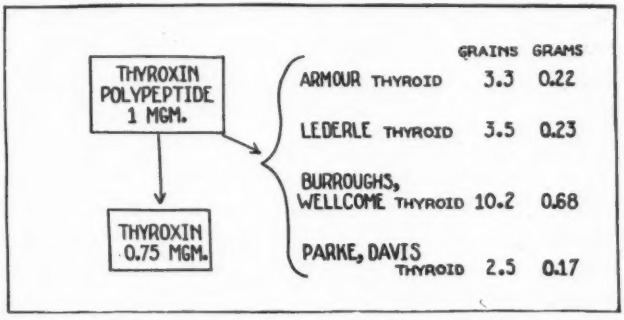

Figure 8. The amount of four different thyroid preparations equivalent to 1 mg. of thyroxin polypeptide or 0.75 mg. of crystalline thyroxin. Burroughs, Wellcome thyroid is expressed in terms of fresh gland; the others in terms of desiccated gland.

tents and the thyroxin iodine contents approximate each other. The most significant comparisons are those in which the total organic iodine contents of the thyroid preparations compared are similar and the thyroxin iodine contents markedly different, or vice versa. These conditions are fulfilled in comparisons numbered 3, 5, 7, 8, 10, 12, 13 and 15 (Table 1). The score in these selected comparisons favors total organic iodine to the extent of 56 against 10 for thyroxin iodine. In other words, the calorigenic action of thyroid gland preparations may be gauged fairly accurately by their total organic iodine content.

It is of interest to note the relative amounts of the various commercial thyroid preparations equivalent to 1 mg. of thyroxin polypeptide or 0.75 mg. of crystalline thyroxin, as charted in Figure 8. Roughly the following were equivalent calorigenically: Armour thyroid (desiccated) grains 1½, Lederle thyroid (desiccated) grains 1½, Burroughs Wellcome thyroid (fresh gland) grains 5, and Parke, Davis thyroid (desiccated) grains 1.

COMMENT

In these studies, three different methods of assaying the calorigenic response produced by thyroid were employed: (1) The administration of small doses daily, by mouth or intravenously, to patients with untreated myxedema; (2) the administration of a single large dose, by mouth or intravenously, to patients with untreated myxedema; (3) the daily administration of small doses by mouth to patients with treated myxedema. The last method was used only to determine the maintenance level of metabolism with different preparations of whole gland. The first method is probably the safest and easiest to employ in untreated myxedema. Further discussion of the method of clinical assay of thyroid activity will be found in the paper by Salter, Lerman and Means (9). Suffice it here to note that the method of assay employed distinguishes between doses of 4.9 and 6.5 mg. of iodine administered in some form of thyroid derivative. The fact is demonstrated in the paper just referred to (9). This accuracy holds both for large single doses and for small divided doses. Considering the crudeness of biological assays in general, this degree of accuracy is quite satisfactory.

The most characteristic feature of the series of thyroid substances studied is the size of the molecules involved. It is difficult to estimate the size of thyroglobulin, but Harington and Salter's (1) analyses indicate that it contains some 800 amino acids in the peptide chain. Under the action of pepsin the chain is reduced to some two or three hundred. The polypeptide, on the other hand, contains no more than three amino acids (one of them thyroxin), and, of course, thyroxin itself is a single amino acid. Thus the data presented above in the charts compare the respective calorigenic responses of whole thyroid (animal); natural thyroglobulin (human); and some of the derivatives of thyroglobulin, namely, thyroxin peptone, thyroxin polypeptide and crystalline thyroxin. The activity of the last three is proportional to their thyroxin-iodine content, which is also their total-iodine content, whereas the activity of thyroglobulin or of whole thyroid is greater than that indicated by their content of thyroxin iodine. Harington and Randall (3) sought to explain this by assuming that optical activity of thyroxin, and possibly also the fact that it is in peptide combination, enhanced its physiologic potency. However, the identity of response produced by pure thyroxin and its polypeptide, when given intravenously in doses of equal iodine content, proves that there is no such enhancement.

All the data presented show that the calorigenic activity of whole thyroid or of thyroglobulin is determined by the total organic iodine content, i.e., thyroxin iodine plus diiodotyrosin iodine. It seems, therefore, that the thyroid contains two hormones—thyroxin and diiodotyrosin. However, the activity of diiodotyrosin is conditioned by its being in combination with thyroxin in the protein molecule, thyroglobulin.

Space does not permit us here to discuss two technical chemical questions which, though extremely pertinent, are relegated to another paper. First, could diiodotyrosin be formed by the decomposition of thyroxin in the course of isolation? The evidence is against its being a chemical artefact. Secondly, how important is inorganic iodine, both in the gland and as formed during chemical manipulation? We believe that it can be neglected for the present purpose, because of its small magnitude.

Some years ago, Harington and Barger (10) suggested, on chemical grounds, that diiodotyrosin is a natural chemical precursor of thyroxin. This view is substantiated by the work of Gutman, Benedict, Baxter and Palmer (11) on changes in the iodine partition of the pathological thyroid glands when iodide is administered. They found that the thyroxin iodine and total iodine contents in untreated "toxic" glands were low. After iodinization, thyroxin increased more in relation to total iodine than did diiodotyrosin so that the thyroxin content of the gland approached normal values. One might infer that the formation of thyroxin was an indispensable step in the production of an active hormone. Whether or not this precursor theory is correct, our work suggests that organic iodine in the gland is calorigenically effective without being converted into thyroxin.

Harington and Randall (3) suggested that thyroid substance employed for pharmaceutical purposes should be assayed in terms of thyroxin, rather than in terms of total organic iodine. This idea has been also voiced by Gutman, Benedict and Palmer (12), who say, "Standardization of thyroid by direct determination of the thyroxin content after the method of Leland and Foster appears to be the most satisfactory solution of the problem. By maintaining the thyroxin content of thyroid tablets within specified limits, one of the most important variables encountered in thyroid medication may be eliminated." Our data indicate definitely that this viewpoint is erroneous and that standardization of thyroid tablets on the basis of thyroxin content is not only unnecessary, but is less accurate (calorigenically speaking) than the determination of total organic iodine (i.e., thyroglobulin iodine)—adulterants being excluded.

Since the initial hydrolysis of thyroglobulin with pepsin to form diiodotyrosin peptone causes the latter to lose its activity, it seems unlikely that much of the thyroglobulin is digested in the gastro-intestinal tract under ordinary feeding conditions. The whole molecule is probably absorbed, for the most part unchanged, as indicated by the experiments of Barnes and Bueno (13). Whether the calorigenic activity is a function of the whole protein molecule or of its iodine-containing amino acids remains to be determined.

These two substances—thyroxin and diiodotyrosin—both having calorigenic activity when combined in the protein molecule might offer a chem-

ical basis for Plummer's (14) two-product theory in exophthalmic goiter. The unusually large calorigenic response produced in one patient by thyroglobulin derived from "toxic" glands is striking, because the thyroglobulin yielded only 25 per cent of its total organic iodine as thyroxin. The effect suggests the possibility that such thyroglobulin may contain one or more abnormally active iodine compounds. That it is not thyroxin is indicated by the fact that thyroxin peptone derived from the same material showed a response in proportion to its iodine content. More observations of this sort are being made. One must also assay thyroglobulin derived from glands of patients who have not received any iodine before operation. At any rate, this type of research affords a systematic approach for investigating the action of the "toxic" gland on a sound chemical and clinical basis.

SUMMARY AND CONCLUSIONS

Chemical advances of the last two decades have yielded two definite chemical fractions in the thyroid. The first, thyroxin, is metabolically active. The second, diiodotyrosin, produces no definite calorigenic response when administered in pure state to myxedema patients. Accordingly it has been assumed that only the thyroxin fraction (acid-insoluble) of thyroglobulin iodine is calorigenically important, although it represents only about one-third of the total iodine. Indeed, it has been suggested that thyroid should be assayed for pharmaceutical purposes on the basis of its thyroxin content alone.

The thyroxin polypeptide of Harington and Salter offered an intermediary substance for comparing the physiological effects of various types of thyroid substance. Daily oral administration of 0.5 mg. iodine in this form in five cases of untreated myxedema produced approximately the same average effect as daily intravenous injections of 0.5 mg. iodine in polypeptide form into such patients. The former data constitute a standard curve of reference.

A single curative dose of 6.5 mg. of iodine as polypeptide in two cases of myxedema showed the intravenous route somewhat more effective than the oral in this large dosage. On the other hand, intravenous polypeptide, in a single large dose, duplicated the effect of crystalline thyroxin given intravenously in equivalent dosage. Since the thyroxin in polypeptide is optically active and the crystalline thyroxin is racemic, it follows that neither optical activity nor peptide linkage enhance the physiologic potency of thyroxin.

The effect of whole gland was tested by daily oral administration of desiccated thyroid. The results were compared with the polypeptide curve of reference. In three cases of untreated myxedema the dose was adjusted to 0.5 mg. of thyroxin iodine. These patients reacted more rapidly than the standard reference subjects. Four other patients received 0.69-0.77

mg. daily of total iodine in the form of desiccated thyroid. The results duplicated or slightly exceeded the polypeptide control curve. Finally, the response of five patients receiving 0.42 mg. of total iodine daily in the form of desiccated thyroid was slightly less than the control group.

Comparative studies of the maintenance dose (in terms of iodine) of six lots of commercial thyroid in twenty cases of myxedema indicated that total organic iodine rather than thyroxin iodine was important.

The results indicate that all of the iodine in thyroglobulin is calorigenically active. They also indicate that thyroid substance should be assayed in terms of total organic iodine rather than thyroxin iodine.

The significance of total organic iodine holds quantitatively not only for whole gland, but also for thyroglobulin and the smaller degradation products thereof containing thyroxin. Assays of thyroglobulin from "toxic" glands on one patient with myxedema and thyroglobulin from "non-toxic colloid" glands on two patients with myxedema indicated an effect which was better referred to the total organic iodine than to thyroxin iodine.

Thyroxin peptone, obtained by peptic digestion of human thyroglobulin gave similar results in two cases, whereas diiodotyrosin peptone, previously fed to these patients, produced no metabolic effect. Therefore the results suggest that diiodotyrosin iodine is calorigenically potent so long as it is part of the thyroglobulin molecule, but loses its activity when separated from the thyroxin iodine fraction.

We are indebted for the human material used in our chemical preparation of thyroglobulin to the kind cooperation of Dr. Tracy B. Mallory of the Massachusetts General Hospital and Dr. Shields Warren of the Harvard Medical School.

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THE ADRENAL CORTICAL THERAPY OF ADDISON'S DISEASE IN CLINICAL PRACTICE

H. LISSER, M.D., F. B. TAYLOR, M.D., AND N. B. LEET, M.D.
SAN FRANCISCO AND OAKLAND, CALIFORNIA

Although Addison, almost eighty years ago, described with imperishable clarity the clinical syndrome which bears his name, and moreover, established its fundamental cause, negligible progress toward its remedy transpired until three or four years ago. This prolonged period of therapeutic failure must be ascribed to the overshadowing significance attributed to the characteristic hypotension and pigmentation, phenomena ascribed to inadequate secretion of the medullary adrenal hormone, epinephrine. Heroic efforts were made to administer this extract orally, rectally and hypodermically, reaching culmination in the so-called Muirhead regime, but with indifferent results. No convincing improvement, arrest of the disease, or material prolongation of life ensued from medullary adrenal therapy.

The experimental physiologists had already provided the explanation for these clinical failures. They had proven beyond dispute that the portion of the suprarenals indispensable for life, is the cortex. One adrenal could be removed completely and the other adrenal also except for a fragment of cortex and yet the animal survived in good health. It was therefore abundantly clear that progress in the treatment of Addison's disease awaited the preparation of potent cortical extracts.

Brilliant success finally crowned the efforts of Swingle and Pfiffner, Hartman and co-workers, and perhaps Stewart and Rogoff, each of whom achieved adrenal cortical extracts which would prolong indefinitely the life of doubly adrenalectomized animals.

In the last three years a fair number of articles have appeared depicting the clinical application of Hartman's "cortin," and Swingle and Pfiffner's adrenal cortical extract. The reference list below includes many of the more important reports. It is not necessary to refer to the authors specifically, in the text, since what follows is not intended to represent a detailed exhaustive review but rather a brief summary and appraisal of the results achieved in Addison's disease. It would be premature to forecast the ultimate scope of adrenal cortex therapy; it may include a diversified usefulness in a wide variety of nervous, muscular and circulatory asthenias. However this may turn out, any considerable clinical trial of the cortex hormone must await further concentration and purification, and, above all, cheaper methods of extraction. The serious obstacle at present is its prohibitive costliness. So long as doses of 3 to 5 cc. or more daily, for many months, and 50 to 100 cc. daily during days of crisis, are necessary to save

life or maintain health, the actual use of this precious hormone must be severely restricted to the very few who can afford it or to such clinics as are richly endowed.

It is obvious that the isolation of this hormone constitutes one of the major advances in endocrinology. Its magical resuscitation of a moribund patient in Addisonian crisis is as convincing and spectacular as the effect of insulin in diabetic coma or the transformation wrought in a myxedematous child or adult by thyroid substance. Enough persons who would have succumbed almost certainly within twenty-four hours have been revived by cortical extracts to banish any doubt as to the specificity or potency of this hormone. It is admitted that occasional failure and death have occurred under cortex therapy, but these can be ascribed, in all likelihood, to one of three factors—inadequate dosage, loss of potency in the preparation employed, or the development of a so-called "irreversible stage" of adrenal insufficiency. Hartman has called attention recently to this peculiar refractory state and points out that repeated relapses to the point of prostration seem to make recovery more difficult, and that death may occur suddenly with little warning. Exacerbation of symptoms constitutes an emergency call for immediate speedy institution of increased cortex dosage.

What have adrenal cortical extracts accomplished in the treatment of Addison's disease? Stated bluntly, they have their limitations. Within the last three years the actual results of this hormone therapy have been recorded in slightly over one hundred cases, which can be summarized as follows:

1. In a considerable number imminent death has been prevented; that is to say, heavy cortex dosage has resuscitated them from a state of crisis. This constitutes its vital and most important effect.

2. The duration of life has been prolonged, in a fair number, well beyond the average under previous methods of treatment.

3. The outstanding benefits derived, aside from maintaining life itself, have consisted in the disappearance of nausea and vomiting with restoration of appetite and a consequent increase in strength and feeling of well-being; namely relief from the asthenia.

4. In some instances a favorable effect has been had on nutrition and weight.

5. In a minority of cases, the blood pressure has been elevated, and pigmentation has faded or vanished; such effects have been exceptional.

6. Whereas blood or urine sugar values are helpful in guiding insulin administration, calcium levels useful in estimating parathormone dosage, basal metabolic rates and blood cholesterol tests a boon in controlling thyroid feeding, no similar "measuring stick" has yet been found which "fluctuates proportionately to the degree of suprarenal insufficiency, and that can be accurately measured" (8). Hence the difficulty in controlling or evaluating therapy in a disease with spontaneous remissions in which the evidence is somewhat circumstantial. It is to be hoped that the recent contributions of Harrop and associates, and also of Loeb, will provide a delicate "check-test" in some phase of sodium metabolism.

7. Both experimental studies and the clinical observations just mentioned, suggest that the hypotension, hypoglycemia, and pigmentation are ascribable primarily to the suprarenal medulla and are, therefore, only occasionally influenced, probably indirectly, by cortical extracts. On the other hand, the asthenia, gastrointestinal symptoms, and the manifestations of shock and crisis are most likely due to cortical deficiency and therefore most consistently alleviated by cortical extracts. However, this does not explain the failure of medullary extracts (adrenalin, epinephrin, etc.) to significantly elevate the chronic hypotension, or convincingly diminish the characteristic pigmentation.

8. The other factor of immediate practical interest is the costliness of cortical extracts. If the one hundred cases previously alluded to are properly segregated, it will be noted at once that they fall into two groups: The first consists of about ninety cases representing the experiences of four major investigations (Harrop, 13 cases; Hartman, 23; Rogoff, 21; Rowntree, 32). The second group comprises scattered reports of 1 to 6 cases. The first group have utilized extracts which they have made themselves (Harrop, Hartman, Rogoff) or with which they have been generously supplied (Rowntree and Harrop at first, by Swingle and Pfiffner). Some of the second group have prepared the extract in their respective institutions (usually by the method of Swingle and Pfiffner), or have been supplied with some through the courtesy of Hartman, or Swingle and Pfiffner. Almost all of the 100 plus cases, therefore, represent generously supported clinical research, rather than the actualities of ordinary practice. The moment one faces the latter situation one is confronted with the necessity of the patient purchasing his own cortical extract. An excellent commercial preparation is available but present methods of extraction culminate in a charge from the retail druggist to the patient of about 6 to 7 dollars for 10 cubic centimeters. Cheney has just reported a most gratifying improvement lasting two years and still continuing in which this product was efficacious in doses of 1 to 2 cc. daily, a cost of approximately 300 to 400 dollars a year. But this experience appears to be exceptional. More often, decidedly larger maintenance doses are necessary, 3 cc. to 5 cc., and this leaves out of the reckoning amounts of 50 to 100 cc. for 24 or 48 hours in time of crisis.

If subsequent study supports the suggestion of Harrop that a high salt intake may markedly reduce the need of cortical extract except in times of crisis, then the problem of costliness will be partially solved. Meanwhile it is only fair to ask whether it is worth while embarking on this treatment in a case of Addison's disease unless the patient is wealthy. Inadequate doses accomplish nothing and merely waste the patient's money. This has been our unhappy experience and this constitutes our reason for recording three cases, each of whom received some cortical extract, obviously insufficient, but they were unable to afford larger quantities. All three died, as was inevitable. The publication of these failures is not intended as a criticism of the clinical value of cortical extracts in Addison's disease when proper amounts can be administered, but we do definitely raise the question as to whether it would not be wiser to give none at all when the patient cannot buy what he needs. We would also suggest that now while the federal, state and county governments are expending enormous sums of money for a great variety of relief measures, including, as always, huge sums for institutions for the insane, that it might be worth considering and urging that life-saving drugs or extracts such as insulin, parathormone, and adrenal cortical preparations, be supplied not only to the very poor but to all persons financialy unable to purchase them. The provision of insulin is becoming a heavy burden to many clinics. Parathormone is used only occasionally and then does not need to be continued indefinitely, but adrenal cortical extracts are the only life-savers in Addison's disease.

REPORT OF CASES

Case 1. An American woman of 50 years complained of increasing fatigue over a period of three years. Menstruation stopped a few months before the languor of her present episode began. For two years she had noticed brown pigmentation of the hands and face, with gradually progressive intensity. One month before coming under observation an illness diagnosed as influenza had confined her to bed for three weeks. At that time she had generalized aching, sweats, fever and malaise without localizing symptoms. Following that illness she had

poor appetite and her languor became more severe. Her weight had decreased twenty pounds in the past year. Blood pressure determinations had been found normal. For many years she had had frequent headaches, fragile finger-nails, and profuse menstrual bleeding, all of which had improved with thyroid therapy instituted twelve years before. She had always been sensitive to cold. She had had no symptoms or illnesses which suggested tuberculosis and had no known tuberculous contacts.

When first seen this patient appeared well-nourished but fatigued, and she had the slaty tan coloring of Addison's disease. She weighed 137 pounds and was 65 inches tall. There was a patchy bluish-brown pigmentation of the gums, with similar discoloration of the labia minora, and a small pigmented area in the rectum a few centimeters above the internal sphincter. The thyroid was not palpable. The heart and lungs were normal. Blood pressure was 108/75. Abdominal, pelvic and rectal examinations showed no significant abnormalities. The lumbar muscles were tense, and firm pressure over the lower lumbar vertebrae elicited tenderness. When first seen she had a normal blood count, normal urine, and a plus 5 per cent basal metabolic rate.

During six months of observation her clinical course was one of increasing weakness, with occasional transient periods of subjective improvement. Because

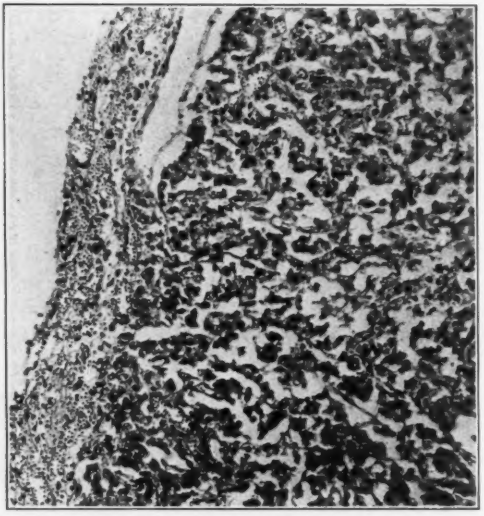

FIG. 1

of this progressive asthenia she was sent to a hospital and eventually confined to her bed. Attempts at walking caused weakness and nausea. For the last four months of her life Eschatin* in doses of 2 to 4 cc. was given subcutaneously every day. Blood-pressure readings sank gradually lower and for many weeks varied from 75 to 85 systolic and 50 to 64 diastolic. Her pigmentation increased. Attacks of nausea and vomiting became frequent. Finally she had a sudden attack of prolonged vomiting followed by a severe chill, delirium, rise in temperature to 104.5° F., and tachycardia. There was marked spasm of the left rectus abdominis muscle but no other localizing sign. Blood pressure dropped to 65/50. She became comatose and died.

At necropsy the adrenals were found to be atrophic and fibrous, especially in the cortices (Fig. 1). Microscopically the cortical cells were decreased in number and there was some fibrous tissue replacement. The medulla showed little abnormality. There was no evidence of inflammation. Retroperitoneal and mesenteric nodes, spleen and thymus were uniformly hyperplastic. There was early degeneration and necrosis of the retroperitoneal nodes. The thymus gland was en-

*Parke-Davis preparation of adrenal cortical extract (by method of Swingle and Pfiffner).

larged, weighing 30 grams, and microscopically appeared very cellular. The spleen was moderately enlarged with marked lymphoid hyperplasia and congestion of the pulp. No evidence of active or healed tuberculosis of the lungs was present. The heart was small and pale with some interstitial fibrosis and cellular degeneration of the muscle fibers. No other significant pathologic changes were noted.

Case 2. This patient was a 50-year-old Chinese woman who was first seen in September, 1931, with the complaint of fatigue, loss of appetite, loss of weight and increasing pigmentation of the skin. Six months previously she became unable to do routine housework because of pronounced weakness and fatigability. Coincidently she noted darkening of the skin about the malar areas, followed in succession by discoloration of the hands and abdomen. Increasing loss of appetite began at the same time, soon followed by occasional nausea and vomiting in the morning. Two years before this illness she had a dry, unproductive cough which disappeared after two months. She had never had chest pain, night sweats, hemoptysis or fever. Two brothers died of pulmonary tuberculosis at ages of 26 and 29 years, respectively. Her parents lived to old age.

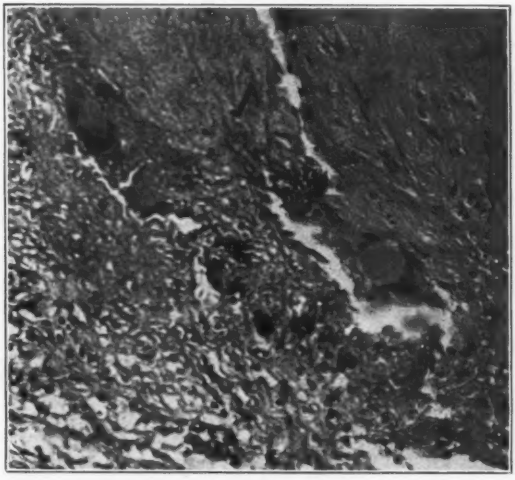

FIG. 2

This little Chinese woman was about 5 feet tall and weighed only 96 pounds. There was diffuse slaty brown pigmentation of the malar areas, the olecranon regions, in the axillae, beneath the finger nails and over the joint surface of the dorsum of the fingers. The upper abdomen appeared banded with similar pigment and there was spotty pigmentation about the eyebrows, on the mucous membrane of the cheeks, the dorsum of the left foot and tibial surface of the left leg. In the lumbar region color changes had been accentuated by application of adhesive tape. The floor of the mouth showed diffuse discoloration. The nipples, areolae and labia majora were dark brown. The thyroid was not palpable. The heart and lungs were normal. The blood pressure was 104/78. There were no other significant physical abnormalities.

Laboratory examinations at the time of initial observation revealed a normal blood count and urinalysis, and a negative blood Wassermann. Stools showed no occult blood or parasites. Two phenolsulphonphthalein tests showed a total two-hour elimination of 60 per cent. Blood non-protein nitrogen was 42.5 mg. per cent, and blood creatinine was 1.5 mg. per cent. X-ray examination of the abdomen revealed no evidence of calcification of the adrenals or deformity of the kidneys. Chest films showed a calcified gland in the left hilus with some thickened pleural markings at the lower part of the upper lobe.

In February, 1932, five months after our initial observation, daily intravenous injections of Eschatin, 1.0 cc., were started. One month later the dose was increased to 2.0 cc. per day. Regular injections of this dose were continued for the period of 10 months until her death. She made daily trips to the office by automobile. She was made to feel slightly stronger as a subjective effect of her therapy. However, her weight gradually decreased to a stationary level between 77 and 80 pounds. Her appetite did not improve. She developed an acute upper respiratory infection, during the third month of active treatment, and became so weak that she had to spend four weeks in bed. In the latter part of this illness she had complete anorexia with three or four days of recurrent vomiting. Five weeks later she had a similar acute illness lasting one week. Weakness and languor continued. She remained at home recumbent the greater part of the time. She had occasional episodes of nausea and vomiting, with frequent pains in the lumbar region and flanks. At times she had substernal oppression on effort. Blood pressure showed no improvement. On December 5, 1932, after 10 months of treatment, she had a sudden crisis, with delirium, incontinence of urine and death.

Necropsy revealed small adrenals, each with a firm cortex. The medullary portion of each gland was soft and showed degenerative changes and coagulation necrosis. There was no clear-cut distinct line between the cortex and medulla. Microscopic study showed typical tuberculous involvement (Fig. 2). The thyroid was small and pale but otherwise normal. The heart was pale and small, with moderate interstitial fibrosis but no other changes. The lungs showed no significant changes. Both kidneys showed marked interstitial fibrosis, with thinning of the cortices. The ovaries revealed excessive fibrosis of the stroma with marked atrophy. The pancreas was normal.

Case 3. An American woman, aged 48 years, was first seen in January, 1931. She had never been robust, but had been a frail, nervous, active person. She had worked successfully at routine office positions for ten years preceding 1930. In January of that year she began to feel excessively fatigued. She became gradually weaker and during the year her weight decreased from 114 to 85 pounds. The most striking symptom was a steady darkening of the skin. Her color finally became dusky tan.

During the third decade of her life she had short attacks of trembling, accompanied by a nervous, exhausted, apprehensive feeling. Her thyroid became enlarged, but she was not considered thyrotoxic by the physician in charge at that time.

The menopause had taken place several years before this illness and was without unusual discomfort. Her menstrual history had been normal. She had never had prolonged bronchitis, chest pain, cough, hemoptysis or chronic fever, and no tuberculous contact was known.

Physically she was a thin woman of 48 years, patiently cheerful, practically bed-ridden for her last two years. The skin was dry and distinctly bronzed. Pigmentation was most marked over the joints, notably on the fingers proximally, elbows, shoulders and knees; also on the face and extending down the neck to the exposed portions of the thorax. It was marked in the creases of the palms. There were many dark freckles on the forearms. The areolae were deeply pigmented. The finger nails were deep brown-black color. The oral, nasal, vaginal and rectal mucous membranes were not abnormally pigmented. There was a soft tumor in the neck to the right of the midline anteriorly, which moved with deglutition. It was approximately 1½ inches in diameter, not attached to the skin, not tender and there was no thrill or bruit. She had no objective evidence of thyroid toxicity. The heart was small. Its sounds, rhythm and rate were normal. The radial arteries were soft and the blood pressure averaged 90/60 on many examinations.

About one year before death, various laboratory tests resulted as follows: Blood count and urinalysis were normal. Stool examinations showed occult blood, but this may have been due to anal bleeding. Gastro-intestinal x-ray examination showed a large appendix but no other abnormal findings. Gastric analysis following histamine showed no free hydrochloric acid. Fasting blood sugar was 92 mg. per cent, and there was a normal response to the glucose tolerance test. Intra-cutaneous tuberculin (0.2 cc. of 1:10,000 dilution) showed a markedly positive reaction. The basal metabolism was minus 18 per cent. Phthalein elimination was 55 per cent in two hours. The blood urea nitrogen was 15 mg. per cent. Blood creatinine was 1.1 mg. per cent, and blood chlorides were 437 mg. per cent.

During 1931 she lost more weight and strength. No specific treatment was attempted until December 11 of that year when 1.5 cc. of Eschatin was given

subcutaneously. This amount was given subsequently at weekly intervals but there was no improvement. On January 9, 1932, on account of extreme weakness and severe pain in the thighs and legs, 6 cc. was given by vein. This may have given transient improvement, but she soon returned to her state of extreme weakness. Four more injections of 1.5 cc. were given intravenously at weekly intervals without effect. Nausea and vomiting began on February 1, and the pain in the thighs became intense. She became rapidly more feeble and expired on February 13, 1932, after an illness of approximately two years.

At autopsy, gross identification of the adrenals was difficult. On dissection they appeared markedly atrophic, and the cortical regions were thin, soft and reticular. The medullary portions of both glands were markedly atrophic, thin and showed excessive fibrosis. Microscopic study showed both cortical and medullary degeneration (see Fig. 3). The cortex was vacuolated and reticular, and the individual cells showed loss of outline and scant cytoplasm. Fibrous tissue replacement of the normal medullary architecture was apparent. The thyroid was small and atrophic with a thick capsule of firm consistency. There was an excessive amount of fibrous tissue and very small amount of colloid storage observed. The heart was small, with pale, thin-walled chambers. The pancreas was normal. The gastro-intestinal tract was normal except for the appendix, which appeared enlarged with engorged superficial blood vessels.

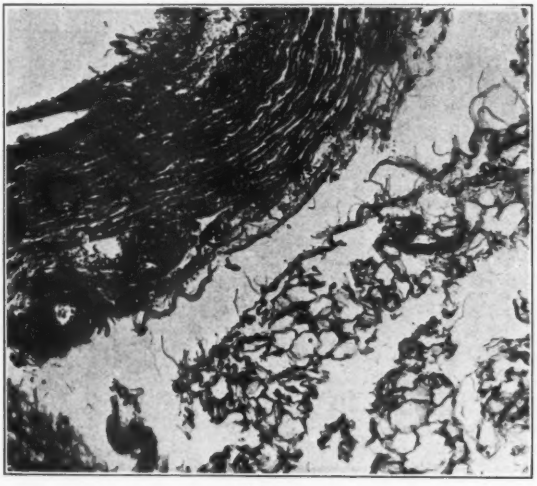

FIG. 3

SUMMARY AND CONCLUSIONS

The results of the use of adrenal cortical extracts in the treatment of Addison's disease are summarized. Such therapy has been recorded in over 100 cases, among which are included three patients of the authors' herein described. These three patients received inadequate amounts of Eschatin and succumbed. Autopsy findings revealed adrenal tuberculosis in one subject and adrenal atrophy in two. In many of the cases in the literature patients were brought back to life when almost moribund; life was prolonged and health vastly improved. The dosage ordinarily necessary for beneficial results was 50 to 100 cc. in times of crises and 2-5 cc. daily as a maintenance dose for months and years.

It is probably not wise to resort to such therapy in ordinary clinical practice unless the patient is able to purchase adequate amounts which may mean an expenditure of $500 to $1500 annually.

The utilization of high salt diets, as recommended by Harrop and associates, may reduce the cortical extract requirements.

Further purification and concentration, or cheaper methods of extraction are most desirable, so that these preparations can receive the clinical application they deserve.

We wish to express appreciation to Dr. Paul Michael for his careful pathological work on the cases here reported.

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TREATMENT OF ADDISON'S DISEASE WITH AN EXTRACT OF THE ADRENAL GLAND

REPORT OF A CASE IN WHICH EXPERIMENTAL RELAPSES AND REMISSIONS WERE BROUGHT ABOUT

M. M. CANTOR, B. Sc., M.D.
AND
JOHN W. SCOTT, M.D.
From the Departments of Biochemistry and Medicine, University of Alberta,
EDMONTON, CANADA

About three years ago, several independent groups of observers (1) (2) (3) presented evidence of having prepared an extract of the adrenal cortex, which, if injected into adrenalectomized animals, was capable of reviving them from prostration and maintaining them in a healthy state indefinitely. About the same time, clinical evidence was presented to show that these extracts gave satisfactory results in patients suffering from Addison's disease (4) (5) (6). It was hoped that a remedy was at hand for yet another fatal disease entity.

Since that time numerous observers have published reports of cases in which adrenal extracts had been used with varying degrees of success. No attempt is being made to review these cases, since in general only immediate results have been given and one is at a loss to evaluate properly the continued benefit of the treatment used. Two of the more recent papers will be discussed, since they have a bearing on the present case.

Baird and Albright (7) have presented four cases of Addison's disease in which Hartman's "Cortin" has been used. Of these, three of the patients are dead, one having been treated for about one year. The fourth patient is alive two and a half years after a course of treatment lasting two and a half months. Particularly interesting is the examination of relapses in these cases. The first patient lived one week after the extract was discontinued. Data presented in the second case indicate that on two occasions when the extract was withdrawn, relapse set in and was pronounced about the third day. Four days elapsed between the time treatment was again instituted, and evidences of remission were quite clear.

Case three was peculiar in that after three months of treatment, withdrawal did not cause a relapse during the two and a half months while the subject was under observation.

In the fourth case the patient had been ill for three and a half years and gave a history of spontaneous remissions. She was admitted in collapse and was given large doses of "Cortin" without any of the usual adjuncts. A remission was brought about, improvement being noted six hours after the first injection. By the fourth day she was almost symptom-free. About 20 cc. daily was the usual dose administered, though 60 cc. daily was given

in relapse, and 130 cc. on one occasion. One cubic centimeter was equivalent to 50 gm. of adrenal cortex. In none of these cases was there any appreciable gain in weight. Blood pressure increase was noted in one instance. The blood constituents, except cholesterol which was increased with treatment, remained unaltered insofar as giving any clue to the results of treatment.

Recently Harrop (8) reported on the results of treatment with Swingle and Pfiffner's preparation of the adrenal gland. Thirteen cases are summarized, two of which are those of patients 3 and 4 of Baird and Albright's series. Of the thirteen, seven patients are dead, five of these having received an adequate supply of a physiologically active preparation. Not any of the seven exhibited gain in weight, although the treatment in four cases lasted for from eight to fifteen months. Relapses were numerous in spite of treatment. In the six remaining cases, including case 3 of Baird and Albright's group, five patients have been treated for from 10 to 19 months. One has been observed for only four months. Improvement was noted in all six, while four only have gained in weight. One patient has had five relapses, three others have had a single relapse. There were no marked changes in blood pressure and pigmentation was only slightly diminished.

The case to be presented is that of a patient who has been under observation for 26 months. Except for the periods during which the extract was withdrawn and replaced with saline, he has been receiving an extract of the adrenal glands regularly. The method of preparation has been modified from time to time and depends upon the solubility of the active substance-complex in organic solvents. The exact procedure of preparation and the results in animal experiments will be reported at a later date.

The immediate results of treatment in this case, with a general review of the literature, were presented about two years ago (9). The earlier history of the case will be dealt with briefly again for purposes of clarity and completeness.

W. B. (No. 12467) male, aged 40, came under observation for the first time on August 29, 1931. A diagnosis of Addison's disease was made, and after treatment he was transferred to the University Hospital on September 21, 1931. He complained of loss of weight, loss of appetite, and weakness. Muscular weakness, preceded by back pain came on about one year prior to admission. This became progressively worse, and in six months he developed a distaste for food. This was followed in a few weeks by gnawing epigastric distress, associated with flatulence, but bearing no relationship to food. About the same time pigmentation was noted. With progression of these symptoms he became quite incapacitated and had to give up work about two months before admission. Within the few weeks just prior to admission he was constantly nauseated, and vomited frequently. His bowels were very irregular, diarrhoea alternating with constipation. The past and family histories were irrelevant.

Physical Examination. The patient was a small, emaciated and very asthenic individual. He was unable to sit up in bed and was apathetic and depressed mentally. The skin over the face, neck, shoulders and extensor surfaces of the arms was brownish in color. The mucous membrane of the mouth was mottled with brownish patches of pigment. The entire skin was extremely dry, with scaly patches on the extensor surface of the arms and legs. The pulse was easily compressible, with a blood pressure of 90/60. The heart showed no abnormalities.

There was no evidence of disease in his lungs on clinical and radiological examination. Apart from slight epigastric tenderness, there were no abnormal physical signs in the abdomen. The neuromuscular system, apart from muscular wasting and weakness, was normal. Laboratory examination at the time showed a red cell count of 4.8 million, haemoglobin 85 per cent; white cells 10,600, with a normal differential count. The blood non-protein-nitrogen was 44 mg. per cent, and the blood sugar 100 mg. per cent. The basal metabolic rate was minus 9. Radiological examination showed no areas of calcification in the region of the suprarenal glands.

The history and the clinical picture were typical of Addison's disease in an advanced stage, and since no tuberculous foci could be demonstrated, was possibly due to primary cortical atrophy. Treatment with adrenal extract was begun on September 14, 1931. The extract was prepared at first according to a method based on the procedures of Swingle and Pfiffner, so the 1 cc. was equivalent to 30 gm. of fresh cortical tissue. The patient was given 20 cc. intravenously in 500 cc. of normal saline, daily for three successive days. Following the second administration he stated that his epigastric pain was less severe and that he felt stronger. On the third day he reported complete relief from his dyspeptic symptoms, and it was noted that he was much more cheerful and interested in his surroundings.

From September 17 to September 21, 1931, he received no extract. Improvement continued up to the latter date, when he again complained of nausea and headache. He was transferred to the University Hospital, but treatment was withheld until September 24, when the symptoms had become quite marked. He was then given daily intravenous doses of 20 cc. of adrenal extract in 250 cc. of normal saline until October 5. There was little change in his condition during the first five days of treatment, except an increase in appetite. On the sixth day, however, there was marked improvement. The dyspeptic symptoms were less troublesome; he was able to eat a full diet and showed a degree of euphoria, which contrasted strikingly with his depressed condition on admission. Three days later the dyspeptic symptoms had entirely disappeared and the pigmentation of the skin was much less than when treatment was initiated. The patient was allowed up, walked about the wards without any evidence of fatigue and stated that he felt perfectly fit. The increase of systolic blood pressure from 72 to 88 and other features of remission are indicated in the table of relapses to follow.

The extract was withheld on October 6, in order to ascertain how long the patient would remain symptom-free. He remained well until October 8, when he complained of pain in the lumbar region, slight nausea, with a return of flatulence and epigastric pain. Treatment was resumed on October 9, and four days later the symptoms had completely disappeared. On October 14, the blood N.P.N. was 30 mgm. per cent, and the blood pressure 94/62. The intravenous administration was replaced by subcutaneous injection, beginning October 12. Two cubic centimeter doses were given twice daily. This daily dose was equivalent to about 600 gm. of fresh cortical tissue or about 13 gm. per kilo of body weight. The patient was discharged, feeling fit on October 23, 1931. During his month's stay in the hospital he had gained seven pounds in weight and showed noticeable diminution in the pigmentation of the skin. Withdrawal of the extract on November 5 was followed by headache on November 7, with weakness, loss of appetite and vomiting on November 8. The symptoms cleared up promptly when treatment was resumed. The daily dosage was halved a week later, and further reduced by the middle of December, until he was receiving 2 cc. daily, that amount being the equivalent of 200 gm. of whole gland tissue.

The patient continued well until January 4, 1932, when a crisis in the disease was precipitated by his taking about 100 grs. of acetyl-salicylic acid with suicidal intent, following domestic estrangement. He was brought into the hospital in a state of collapse. He was very weak and constantly nauseated. The blood pressure was 90/50, the temperature was 96.2, the CO_2 combining power was 24 Vol. per cent, and there was acetone and salicylates in the urine. Since he had been receiving extract regularly, it was felt that no increase in amount was necessary, and the usual 2 cc. dose was continued. As an adjunct, he received a single intravenous administration of 700 cc. of 5 per cent glucose in saline solution. His recovery in four days was marked by the same stages that accompanied his recoveries in previous relapses. The systolic blood pressure rose to 100 on occasions, but fell again to 90. The temperature rose to normal on the second day following admission.

On February 4, 1932, following a period of four weeks, during which time he was symptom-free, the extract was withdrawn and sterile water substituted. The temperature became subnormal (96°) on Feb. 6, and anorexia, nausea and

vomiting developed and became marked on February 8. He complained of backache and weakness. The sterile water was replaced with extract on February 10, and he became symptom-free on February 13. On March 9, while the patient was at home, it was decided to produce a relapse, in order to test the potency of a special fraction in crisis. The extract was again withdrawn and sterile saline substituted. Within four days he was bedridden. Anorexia developed first, and was followed by nausea and vomiting. On March 13, the symptoms became quite marked. The saline was now replaced by an equal amount of a concentrate of the extract to be tested. There was no appreciable difference in the outward appearance of any of the fractions he had been receiving. This concentrate was administered on five successive days. By March 19, his condition became quite alarming. Nausea was very pronounced and vomiting intractable. He was extremely weak and suffered from severe pain in the back and headache. Morphia was required to alleviate his suffering. The systolic blood pressure had dropped to 68. He was admitted to the hospital and 3 cc. of the concentrate, together with 250 cc. of 5 per cent glucose in saline was administered intravenously. On the following day, 4.5 cc. was administered intravenously in 500 cc. of solution. There was no visible improvement. At 8 P.M. on the 20th, 5 cc. of a known potent fraction was given intravenously. This was repeated on the two days following. Signs of amelioration were evident on the 21st, and on the 22nd he was practically symptom-free. The dose was reduced to 2 cc. daily, given subcutaneously. His temperature, which was below 96°F on admission, rose to within normal limits. The blood pressure rose to 88/50 on the 21st, and the pulse rate, which had been about 130, fell to 76.

On March 23, following catheterization during the period of collapse just described, he developed an acute urethritis and cystitis. The symptoms of Addison's disease became aggravated, and he was very weak. The temperature was elevated and haematuria was marked. On March 24, the dosage of extract was increased to 5 cc. daily, given intravenously. He became progressively weaker, and on March 27, he was given 13 cc. and a further 13 cc. in the next two days. On March 30, his condition was greatly improved. He voided voluntarily and became symptom-free on the 31st. The extract was then withdrawn. He remained well and felt quite fit until April 7. On that date symptoms returned and became quite marked on April 8. He was given 3 cc. of the extract on the 8th. On April 9, his appetite had improved and he became symptom-free on the following day, and was discharged April 11. He was instructed to continue with 2 cc. twice daily.

Although he had continued on 2 cc. of extract twice daily, he returned to the hospital on May 2 in a weakened condition. There had been an exacerbation of symptoms for a few days prior to admission. Examination at that time revealed an acute pharyngitis in addition to the usual findings in relapse. The amount of extract he was receiving was not increased. On May 5, three days after admission, the temperature, which had been only slightly elevated, rose to 103° F. There was severe abdominal pain. Physical examination suggested a bronchitic process. The dosage of extract was increased so that he was given 12 cc. daily intravenously on May 5, 6 and 7. On the 6th, he complained of pain in the lower chest. Cough, productive of very purulent sputum, developed, and the patient became progressively worse. Treatment was continued, and on May 9, improvement was noted. The cough persisted for some time, but his health became progressively better, and he was discharged on June 12, after a thorough investigation for a possible tuberculous focus in the lungs. He remained well until June 30. On that date, due to some irritation at the site of injection of the extract in the thigh, the patient stopped treatment. An abscess developed at the site, and he was admitted to the hospital for treatment of the abscess, as well as the symptoms of Addison's disease, which had recurred, following his withdrawing the treatment. Without increasing the usual dosage, treatment was again instituted, and he was symptom-free by July 8. He tolerated the minor surgical procedure of draining the abscess without increase in dosage. Healing was excellent. Re-examination of his genito-urinary tract showed no tuberculous focus. He was discharged on August 13. He was re-admitted August 23, 1932, with another abscess in the thigh and symptoms of withdrawal. The abscess was incised and drained. Following admission, he remained weak and complained of epigastric distress, even while he was receiving treatment. There were occasional attacks of vomiting. The symptoms, while not severe, became quite marked, and pigmentation became deeper when the extract was withdrawn, as was done between August 28, and September 3, and between September 11, and September 14. The symptoms disappeared within five and three days respectively after treatment was again instituted.

From mid-September, 1932, until January, 1933, he continued in a fair state of health, receiving 2 cc. of extract subcutaneously daily (equivalent to 80 gms. of whole gland). At this time the concentration of extract was reduced, so that 1 cc. was equivalent to 45 gms. of whole gland. There was no change in his condition as a result of this diminution. On April 5, sterile distilled water was substituted for the extract usually sent out to him. Three days later, his wife phoned to say he was getting weak and was quite nauseated and that vomiting was beginning to become pronounced. He was seen on April 9. His blood pressure was 100/60; pulse fair in quality. He complained of nausea, but vomiting, while present, was not very marked. Sterile water injections were continued. The symptoms gradually increased in severity, so that by April 19 he had become quite weak. The sterile water was then replaced by an extract in the same manner in which it had been withdrawn, there being no difference in the outward appearance of the substituted samples. On April 22 the patient was apparently well again, and has continued to remain so. When he was seen on August 26, 1933, he was getting along quite well. working in his garden and taking moderately long walks. He had gained about 20 lbs. in weight, but his blood pressure had not

Photograph of W. B., on June 1, 1933, showing disappearance of normal skin pigment, after 20 months of extract treatment.

altered. Pigmentation of the skin was greatly diminished and was absent from the mucous membranes.

Since about April, 1933, he has noticed irregular white patches developing and enlarging over the skin surface of his chest, arms, neck and lower back. These became progressively larger for a time. (See photograph.) A biopsy made on one of these skin patches showed that there was no activity in the basal pigment layer, and, indeed, extremely little normal pigment.

Comment. It is, of course, impossible to detail the day-to-day observations in the case described. The significant findings are tabulated in the following chart in which the periods of relapse are summarized.

In all, 14 relapses have occurred during a period of more than 26 months, excluding the collapse on admission. Eleven of these were induced by withdrawing the extract and substituting sterile saline in six. Of the

TABLE OF RELAPSES

No.	BEFORE RELAPSE			Cause of Relapse	Ext. Stop. Date	Interval Till Relapse Days	CONDITION DURING RELAPSE			Duration Without Treatment	Treatment Started, Date	Days Till Symptom Free	Amount Extract Required	CONDITION IN REMISSION		
	General Condition	Temp.	B. P.				General	Temp.	B. P.					General	Temp.	B. P.
1	As on date of admission.	96.	82/60	Collapse on admission.	.....	.....	Anorexia, nausea, vomiting, diarrhea, weak, pigmented, etc.	96.	82/60	.....	14– 9–31	2–3	60 cc.	Euphoria, no distress. Appetite good.	98.4	94/68
2	No complaints.	98.4	96/68	Withdrawal.	17– 9–31	4	Epigastric distress, weak, feels cold.	96.	72/54	7	24– 9–31	6	120 cc.	No complaints.	98.2	90/60
3	Up and about, quite well.	98.3	90/62	Withdrawal.	5–10–31	3	Dyspepsia, weakness, deepened pigmentation.	96.[1]	82/60	5	10–10–31	5	80 cc.	Quite well. Decreased pigmentation.	98.2	96/64
4	Symptom free, working.	98.	88/50	Withdrawal.	5–11–31	3	Anorexia, weak, vomiting.	.....	72/54	5	10–11–31	2	12 cc.	Feels well, working.	.....	99/60
5	Quite well, even in cold.	.....	90/50	Attempted suicide, C 100 gr. Aspirin.	4– 1–32	1	Nausea, vomiting, collapse.	96.[2]	90/52	.....	5– 1–32	4	8 cc.	Up and about. Quite well.	98.4	100/74
6	Quite well.	98.2	102/68	Withdrawal, subst. C water.	4– 2–32	4	Anorexia, nausea, quite weak.	97.	90/60	6	10– 2–32	3	6 cc.	Fairly well.	98.	90/60
7	Up and about, quite well.	.....	94/62	Saline substituted, then test fraction.	9– 3–32	4	Anorexia, severe emesis, backache, weakness.	95.[2]	88/48	10	20– 3–32	3	11 cc.	Symptom free.	99.	90/60
8	Fairly well.	98.2	90/50	Acute cystitis, 23–3–32.	.....	.....	Severe dyspepsia, collapse.	102.[2]	70/40	.....	Increased 24– 3–32	7	45 cc.	Quite fit.	98.4	85/45
9	Up and about. Quite well.	98.2	90/60	Withdrawal with substitution.	1– 4–32	6	Loss of appetite. Weakness.	97.2	90/60	6	8– 4–32	3	9 cc.	Fairly well.	99.	88/50
10	No complaints.	98.3	90/50	Acute broncho-pneumonia 2–5–32	.....	.....	Severe crisis, dangerously ill.	102.	80/58	.....	Increased 5– 5–32	4	36 cc.	Greatly improved. Out of danger.	98.	98/70
11	Quite well.	.....	82/55	Stopped extract himself due to irritation.	30– 6–32	4	Nausea, anorexia, weakness, confined to bed.	102.2	90/52	8	8– 7–32	5	10 cc.	Minor operation. Well sustained.	98.2	96/60
12	Quite well.	.....	.....	Stopped extract due to irritation.	21– 8–32	2	Epigastric distress, occasional vomiting.	96.	.....	3	24– 8–32	.....	.....	Not symptom free.	97.	.....
13	Not very well.	97.	.....	Withdrawal with substitution.	28– 8–32	3	Increased distress and weakness.	95.3	.....	6	3– 9–32	5	10 cc.	Minor operation. Well sustained.	98.	.....
14	Fairly well.	98.	.....	Withdrawal with substitution.	11– 9–32	3	Mild symptoms of dyspepsia and weakness.	96.1	.....	3	14– 9–32	3	6 cc.	Fairly well.	98.	.....
15	Quite well.	98.2	.....	Replaced with saline.	5– 4–33	4	Nausea, vomiting and weakness.	.....	100/60	12	18– 4–33	4	8 cc.	Continues well.	.....	100/60

remaining three, two were brought about by intercurrent disease and one by poisoning due to salicylates. It will be noted that in each instance withdrawal of the extract was attended by the appearance of symptoms in from three to four days. Appetite failed and was followed by nausea, vomiting and epigastric distress. These became progressively worse and were accompanied by weakness and occasionally deepened pigmentation. Temperature was depressed and blood pressure occasionally lowered. After treatment was instituted, nausea and vomiting were first to disappear and temperature rose to normal, usually on the following day. Anorexia became lessened and epigastric distress vanished about the second or third day. The periods of experimental withdrawal ranged from three to twelve days. Throughout the course of treatment the blood pressure was not altered appreciably, except during the height of the period of relapse when it was low. The temperature was usually subnormal during the relapse, but rose quickly to normal when treatment was instituted. There has been a gain in weight of about twenty pounds since the patient was first seen. He is now able to get about the house, work in his garden and take short walks. His appetite is good and he has no dyspeptic symptoms. Pigmentation has markedly decreased and the normal skin pigment has disappeared in patches. He has been tided over two rather severe acute intercurrent infections, acute broncho-pneumonia, acute cystitis, and has tolerated two minor surgical operations. Healing was rapid and good in both instances.

DISCUSSION

Throughout this paper we have used the term adrenal extract instead of cortical extract advisedly, since, while it is true that the cortex is the essential part of the gland as regards life, the extracts used were prepared from the whole gland. There is quite sufficient evidence to show that the cortex in the fresh state contains no adrenaline, but none whatever to indicate that the medulla is entirely functionless in the elaboration of the substance or substances stored in the cortex and essential to life. Indeed quite the contrary is suggested by the anatomical structure of the gland, and the general considerations presented recently by Harrop (8).

This present case presents features which serve well to demonstrate the analogy between the response to treatment in Addison's disease and other endocrine insufficiencies, such as diabetes mellitus. Indeed, the effect of treatment in all instances of relapse was as definite and dramatic as that of insulin in diabetic coma. As with insulin, it is quite evident that the quantity of extract must be generously increased during the course of infections and in relapse due to withdrawal. As in diabetes, too, the patient with Addison's disease is very likely to develop abscesses more readily than a normal individual, and is also more likely to succumb to mild intercurrent infections.

A point of interest in connection with the suggested relationship between the adrenal cortex and the gonads, is the statement advanced by the patient that he had regained his sexual vigor since he had been under treatment.

The leucodermia which has developed in this patient may be coincidental or due to the extract. The decrease in pigmentation during treatment was often noticed within a few days after the administration of extract was begun. It was often sufficiently noticeable to be commented upon by relatives of the patient or members of the staff who had seen him at somewhat longer intervals than his immediate attendants. The pigmentation has lessened with the progress of the case and has approached normality. The pigmentation of the mucous membranes disappeared entirely during treatment, but usually recurred during relapses. Pigmentary changes have run quite parallel to the changes in the general condition, diminishing with improvement and increasing with relapse. It has been suggested by Levy-Simpson that these changes may be due both to increased dissolution or decreased deposition of pigment. The depigmentation beyond the degree of normal skin pigmentation, which has undoubtedly occurred in the leucodermic areas in this patient, would suggest that, in this case at least, the factor of dissolution was the more pronounced of the two.

It is felt that the diagnosis in this case of adrenal cortical atrophy is not circumstantial, and that the evidence presented of repeatedly induced relapse and remission is as incontestable a test for the potency of an extract as is the biological test on animals. It is interesting to note, too, that neither the degree to which the patient sunk in relapse nor the number of times during which a relapse had been induced previously, had very much to do with the manner or time in which the remission was brought about. In view of these observations, it is difficult for us to subscribe to Hartman's suggestion of irreversibility of the process in repeated relapses (10).

SUMMARY

1. Some late results in the prolonged treatment of Addison's disease with extracts of the adrenal gland are reviewed briefly.

2. A case of Addison's disease is presented in which treatment has been continuous for more than 26 months and in which experimental relapse and remission were induced 11 times without any lasting ill-effects.

3. It is suggested that the term adrenal extract is more appropriate than cortical extract until more definite information regarding the site of elaboration of the active substance or substances is available.

4. An analogy is drawn between adrenal insufficiency and other endocrine insufficiencies, particularly diabetes mellitus.

5. Return of sexual vigor in this case brings out the relationship between the adrenal cortex and the gonads.

6. The development of leucodermic patches in this case supports the suggestion that decrease in pigmentation during remissions is due to dissolution of pigment in the skin rather than decrease in deposition of pigment.

7. Neither the number of relapses, the severity of the symptoms nor their duration, affected the regularity of the response to treatment suggesting the absence of the so-called "Irreversibility of the process in repeated relapses."

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PARATHYREOTROPIC ACTION OF THE ANTERIOR PITUITARY: HISTOLOGIC EVIDENCE IN THE RABBIT

SAUL HERTZ, M.D.* AND ALFRED KRANES, M.D.†
From the Medical Service and Metabolism Laboratory, Massachusetts General Hospital
BOSTON

In December, 1932, we received a preliminary impression that intramuscular injections of saline emulsions of anterior lobes of beef pituitary glands gave rise to enlargement and increased vascularity of the parathyroid glands of rabbits. As far as we could discover at the time, no previous reference had been made to such an effect of anterior lobe substances. We, therefore, undertook more extensive experiments to collect data on the gross and microscopic anatomy of the parathyroid glands of rabbits under treatment with various anterior lobe substances, pregnancy urine and control injections of brain tissue emulsions.

PLAN OF EXPERIMENTS AND METHODS

Rabbits of the same age, sex and strain (blue bevern) were used in each of our early experiments. These factors were later varied singly; and since it was found that neither sex, age nor strain had any modifying effect, females of mixed strains were used in later experiments. Rabbits were segregated as to sex in order to avoid the complicating factor of pregnancy. Animals used in individual experiments ranged from 10 to 22 weeks of age. They were fed on rations of oats, greens, fresh carrots and occasional additions of cow's liver. No cod-liver oil was added. Normal control animals (untreated) were healthy and survived in excellent condition in the hygienic atmosphere of the animal farm except for a rare attack of diarrhoea in the younger members of the colony.

Intramuscular injections were carried out with sterile precautions after preparation of the skin with alcohol. The materials listed below were assayed for a qualitative effect on the parathyroid glands. Animals were kept under the conditions of the laboratory for a preliminary control period before any injections were given.

Fourteen animals received saline suspensions of fresh bovine anterior lobes which were obtained daily from the slaughter house directly after the death of the cows. The pituitary glands were kept cold and the anterior lobes were dissected free within one to three hours. These were then ground in saline with mortar and pestle. Care was taken to have all the utensils sterile. When the material was ground to a consistency fine enough to pass through a large bore needle it was diluted with saline so that 5 cc. was usu-

*Dalton Scholar and Graduate Assistant in the Department of Medicine, Massachusetts General Hospital.
†Assistant Resident in the Department of Medicine, Massachusetts General Hospital.

ally equivalent to the tissue obtained from half of an anterior lobe. This was then drawn into a syringe and injected into the thigh muscle of the rabbits.

Three animals received heated suspension of this material (boiling water for 5 to 10 minutes). Two animals received emulsions of brain tissue prepared in a similar fashion. Twelve animals were kept under the same housing conditions, but received no injections.

The above materials were coarse and not sterile. They frequently caused local abscesses. In subsequent experiments, sterile extracts were used. They were prepared as follows:

1. Saline emulsion of anterior lobe was passed through a Seitz filter for sterilization. Two animals were treated with this extract in daily dosage equivalent to 1.5 grams of tissue, for five days.

2. Acid extraction of anterior lobe was carried out with acetic acid (pH 4.8 to 5.0) and six animals received daily injections of 1 gram equivalent for from three to 28 days.

3. Alkaline extraction was carried out with sodium hydroxide at pH 8.0 to 8.5, and sterilization was obtained by passage through a Seitz filter. Six animals received the equivalent of 1 gram of tissue of this material in daily dosages for four to six days.

4. Acid extraction was carried out following preliminary alkaline extraction and used in two animals in dosage of 1 gram equivalent of tissue, for four days.

5. Alkaline extraction, following preliminary acid extraction, was performed and this material was administered to one animal in dosage of 1 gram equivalent for six days.

The above sterile filtrates were kept on ice for a period of seven to eight weeks (at pH 7.4) and used for the injection of four additional animals, as an assay of stability under these conditions.

Progynon, Antophysin, Thyreotropic Hormone and Parke-Davis Growth Hormone were injected into a group of seven animals. Pregnancy urine, prepared as for the Friedman test, was injected into five animals for one to four days. Urine of two non-pregnant individuals was similarly injected into control animals.

Animals were killed by bleeding, pithing or etherization. The parathyroid glands were removed immediately after death of the animals and fixed in Zenker's solution and 10 per cent alcoholic formalin. The usual methods of dehydration and paraffin imbedding were used and sections were cut to a thickness of 5 to 7μ. Haematoxylin-phloxin and phloxin-methylene blue stains were employed.

RESULTS

The clinical picture of the rabbits which received active pituitary materials was strikingly different from that of animals receiving control injec-

tions or of the untreated animals. Figures 1A and 1B illustrate two littermate animals which were treated respectively with identical dosages of fresh and heated saline emulsions of beef pituitary glands. The loss of weight, muscular weakness and atonia, which the animal in Fgure 1A showed, were seen in varying degrees in all animals which received injections of active pituitary extracts.

Notes were made as to the size and gross appearance of the parathyroids. Microscopic descriptions were made of each gland sectioned but will not be included in this report. They are, however, the basis for the following descriptions.

Anatomy of the Normal Rabbit's Parathyroid Gland. The rabbit has two main parathyroid glands. They are situated lateral to the internal carotid artery and at varying distances from the inferior-lateral aspect of

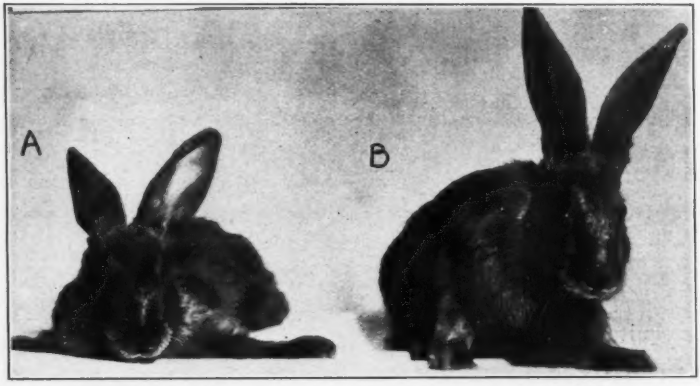


Figure 1. A—Photograph of rabbit No. 22, showing typical prostration and muscular atony of an animal which received injections of emulsions of fresh bovine anterior pituitary glands. B—Photograph of rabbit No. 9, an animal which received injections of heated emulsions of bovine anterior pituitary glands.

each thyroid lobe. There is considerable variation in their size, but their shape is quite constant. They are rounded at their upper poles and measure about 1 to 2 mm. in breadth at that, their widest point. They taper longitudinally for about 0.5 to 0.75 cm. to become attached to the carotid fascia in which they are enveloped. The main parathyroids are occasionally constricted at their mid-point, giving the impression of being bilobed. They are at times situated quite low in the carotid sheathe, close to the mediastinal space.

Glands were not weighed in our gross study because it is our belief that such determinations are subject to too great an error. Differences in amounts of capsule, fat, fascia, thyroid and muscle to various glands in microscopic sections indicated some of the sources of such error. It is further our belief that these measurements are vitiated by varying degrees of

evaporation as well as the inevitable differences in the nutritional state of the animals.

Normally, the parathyroid gland is white and glistening. It may also have a pink color, but as a rule is not injected on its flat presenting surface. The larger blood vessels may be visible.

The normal accessory parathyroid glands are inconstantly and rarely seen at post-mortem, but were found quite regularly in our miscroscopic examinations of the thyroid glands.

Microscopic Examination. The appearance of a normal rabbit's parathyroid under low magnification (x 100) is illustrated in Figure 2, Photomicrograph A, which is that of a section of the parathyroid gland of Rabbit 622, an untreated animal. The striking feature of the section is the

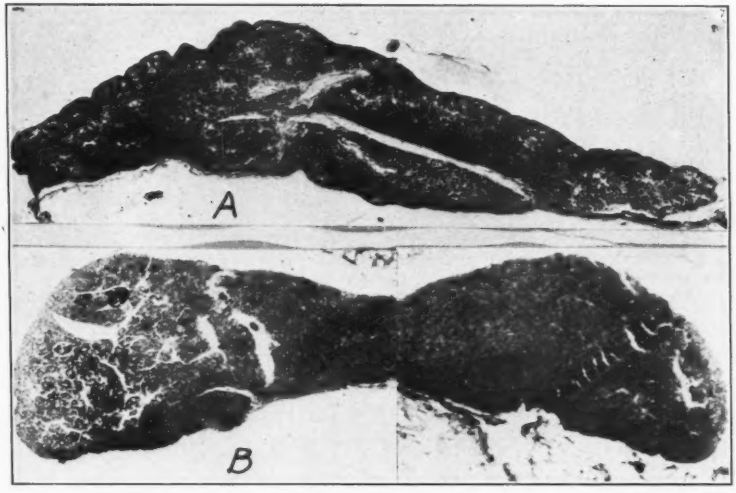


Figure 2. A—Photomicrograph (x 100) of the parathyroid gland of a normal untreated animal (No. 622). B—Photomicrograph (x 100) of the parathyroid gland of an animal which had received 5 daily injections of an acid extract of bovine anterior pituitary glands (No. 699).

prominence of the interalveolar septa. Its fenestrated structure is in distinct contrast to the solid and dense appearance of a similar section of the parathyroid gland of a pituitary treated animal 699 (see Figure 2, Photomicrograph B).

Examination at higher magnification (x 430) reveals that the normal parathyroid is not uniform in its structure. The peripheral zone of alveoli is densely packed beneath the fibrous capsule of the gland. In this area the alveoli are smaller than in the remainder of the gland, but the individual cells are larger. Vacuolization and a rare mitotic figure, when found in the glands of normal animals, are situated in this zone, the "Randpartie" of Erdheim's descriptions. The centrally located alveoli vary in size and shape. They contain from one or two to ten cells per alveolus. They are

crescentic in shape and are made of one or, at most, two cell layers. The range of alveolar size under normal conditions is given in Table I, which also presents measurements of cell, nuclear and vacuolar diameters in these same normal parathyroid glands (Animals 622, 700 and 606). These and all measurements included in this report were made with graduated ocular at oil immersion magnification (x 970).

Figure 3A is a camera lucida drawing, illustrating a normal parathyroid gland as seen under oil immersion magnification (x 970). It shows widely separated alveoli of small, though not uniform size. The cells are small and mitoses, pyknoses and vacuoles are absent or rare. The alveoli are one cell deep and infolding of the epithelium is not seen. The stroma is fairly prominent. (Compare with 3B.)

Anatomy of the Parathyroid Glands of Animals Treated with Active Pituitary Substances. Parathyroid glands from animals treated with various types of anterior pituitary preparations were examined. The details of extractions employed and of dosages used are indicated below.

TABLE I

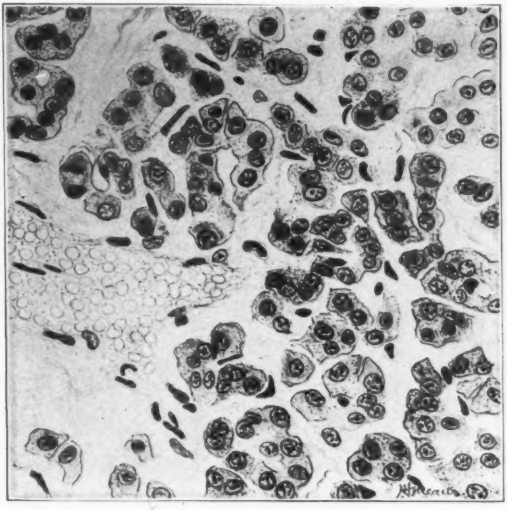
RANGE OF ALVEOLAR, CELL AND NUCLEAR SIZE IN THE PARATHYROID GLANDS IN THREE NORMAL RABBITS AND IN THREE REPRESENTATIVE RABBITS TREATED WITH ACTIVE ANTERIOR PITUITARY SUBSTANCES

Rabbit Number	Alveolar Range mm/100	Cell Range mm/100	Nuclear Range mm/100
	NORMALS		
606	7 x 7 to 70 x 77	4.2 x 5.6 to 7.0 x 8.4	2.8 x 2.8 to 4.2 x 5.6
700	7 x 28 to 56 x 70	5.6 x 7. to 5.6 x 9.8	1.4 x 1.4 to 4.2 x 5.6
622	7 x 14 to 42 x 49	4.2 x 8.4 to 5.6 x 9.8	4.2 x 4.2 to 4.2 x 6.3
	TREATED		
699	28 x 35 to 42 x560±	8.4 x14. to 9.1 x16.8	2.8 x 5.6 to 5.6 x 5.6
624	11 x 14 to140 x238±	5.6 x12.6 to 7. x14.	4.2 x 4.2 to 5.6 x 7.
683	21 x 21 to196 x350±	7. x 7. to 5.6 x14.	4.2 x 4.2 to 5.6 x 8.4

On gross examination it was found that the parathyroids of pituitary treated animals were larger than those of the reference controls. This was, however, not invariably true. More constant than the increase in size was the finding of vascular engorgement in the glands of injected animals. For the most part, there existed considerable correlation between the degree of vascularity, size, color and the microscopic appearance of the glands.

The most significant differences between the normal and injected glands were found on microscopic examination. Figure 2B is a photomicrograph (x 100) of the parathyroid gland of Animal 699. This animal received five daily intramuscular injections of an acid extract of beef pituitary containing 1.3 grams of anterior lobe tissue per dose. A comparison with the normal gland at the same magnification (Figure 2A) shows the compact arrangement of the glandular elements, the disappearance of the wide inter-

alveolar septa and the general increase in epithelial cellularity. The appearance of this same section of parathyroid gland from Animal 699 under higher magnification is illustrated in Figure 3B, which is a camera lucida drawing under oil immersion (x 970). It is to be compared with Figure 3A,



an entirely similar drawing of a normal untreated animal's parathyroid gland (i.e., No. 606, a reference control). Figure 3B shows a marked

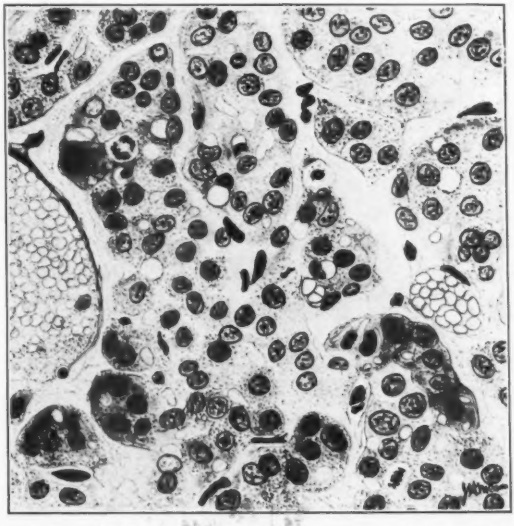


Figure 3. A—Camera lucida drawing of the appearance of the parathyroid gland of a normal untreated animal (No. 622) at oil immersion magnification (x 970). B—Camera lucida drawing of the appearance of the parathyroid gland of a pituitary treated animal (No. 699) at oil immersion magnification (x 970).

increase in cellularity, enlarged alveoli, high cells and active growth as evidenced by numerous mitotic figures (3 mitoses and 2 pyknoses in a single field). Large vacuoles in the cells indicate a probable increase in secretory activity. The blood vessels are increased in number as evidenced by the numerous endothelial cells interspersed in the perialveolar spaces as well as between the alveolar cells. The cell nuclei are lighter staining and larger than in the normal gland. Pyknoses are common. The nuclei are spaced farther apart than in the normal parathyroid because of the increased size of the cells.

It would require a description of each gland studied to give an impression of the intermediate stages between the normal parathyroid histology and that of the hyperplastic gland illustrated in 3B. At this point, however, we wish to call attention to the difference in histological changes in glands which have been rendered hyperplastic at different rates. It is our impression that animals which were subjected to large doses of active material over a short period of time showed parathyroids with marked increase in number and change in arrangement of cells without much increase in size of cells. This type we have designated as "conglomerate alveolar" or "mulberry type" of hyperplasia in our own discussions. An example of this type is given in No. 683 with measurements of the acini, cells and vacuoles (see Table I).

A more chronic treatment of the animal gave rise to the type of hyperplasia that is illustrated in Animal 699 (see Table I and Figure 3B). This type is characterized by moderately increased number of cells, but with predominant enlargement and vacuolization of cells. Mitoses were seen in both types, but more readily in this second type which we have designated "large vacuolated cell type." We have seen both of these histological pictures in tumors removed from human cases of hyperparathyroidism at the Massachusetts General Hospital.

Saline suspensions, acid and alkaline extracts, pregnancy urine, Antophysin (Winthrop Company), Progynon, Parke-Davis Alkaline Growth Hormone, and Thyreotropic Hormone (Schering and Kahlbaum) were found to produce varying degrees of parathyroid hyperplasia. Brain tissue emulsions, heated pituitary suspensions and urine of non-pregnant individuals had no effect on the parathyroid histology. The control animals which received no injections showed none of the changes described above. Occasional glands in the control group showed increased vacuolization, but did not satisfy the other criteria for hyperplasia. Extracts which were assayed after a lapse of seven to eight weeks showed that the parathyreotropic effect was retained to some extent at ice box temperature and pH 7.4.

DISCUSSION

The extensive literature which has accumulated in recent years on the relationships of the anterior pituitary to the other endocrine organs con-

tains but meagre clinical and experimental reference to the parathyroid glands.

In his monograph on the pituitary body Cushing (1) called attention to a group of cases showing primary hypophyseal disease with associated alterations in other members of the endocrine series. In his more recent writings (2a, 2b), he has delineated a clinical syndrome clearly enough to enable the prediction of the port-mortem finding of an hypophyseal basophilic adenoma.

In 1912, Schmorl (3) mentioned a case of typical osteitis fibrosa cystica in which he found the association of a large basophilic adenoma of the hypophysis with diffuse adenomatous hyperplasia of the parathyroid glands. Schmorl did not suspect a relationship between the two adenomatous growths, but Molineus (4), in reporting the same case in greater detail, made the suggestion of such a possible relationship. He quoted Fischer's contention that "acromegaly was absent in this case because of the disease in other glands (i.e., parathyroids)." The frequent association of acromegaly with eosinophilic tumors of the pituitary was not clear at that time.

Erdheim (5) stated that he had seen the association of osteitis fibrosa cystica and basophilic adenoma of the pituitary in two necropsied cases.

Lloyd (6), in 1929, reported a case from the Johns Hopkins Hospital Department of Pathology, which presented the post-mortem findings of tumor-like enlargements of the parathyroids and islets of Langerhans in association with hypophyseal tumor (type not given). No clinical data were available in that case from which to decide whether the parathyroid or islet tissue had had excessive functional activity during life.

In Cushing's descriptions of patients having pituitary basophilism, terms such as kyphosis, lordosis, multiple fractures, marked weakness, polyuria, decrease in height, renal change, albuminuria and so forth are frequently found. On the pathological side, "bones soft enough to cut with a knife," osteoporosis, compression of vertebrae and healed fractures were commonly encountered. All these things are now known to be among the classic manifestations of hyperparathyroidism.

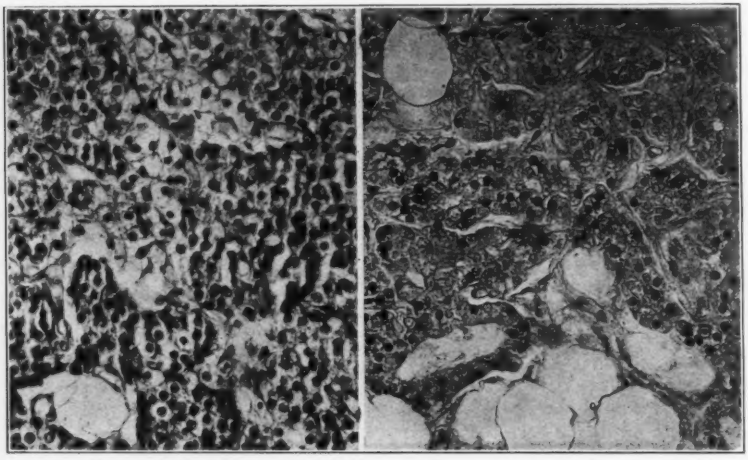
In Case No. 9 of Cushing's series (2a), a single parathyroid was examined and was reported as showing "an increase of fat and connective tissue." However, in a personally autopsied case, Dr. Cushing reported two parathyroid glands as being slightly enlarged (measured 7x5x2 mm. and 10x5x3 mm.). Histological examination was reported as follows: "Essentially normal apart from the fact that two-thirds of the gland is composed of fat" (2b). On review of a section with Dr. Cushing, we were convinced that the gland in question was truly hyperplastic and satisfied the criteria of Erdheim, which were used throughout our study of animal parathyroid glands.

Microphotographs of a normal human parathyroid and of the gland of Dr. Cushing's case are presented in Figure 4 with his kind permission.

They give additional histological evidence of a parathyreotropic effect of the anterior pituitary.

From the experimental point of view, P. E. Smith (7) described the disabilities caused by hypophysectomy in the rat. He mentioned briefly that the parathyroid glands, among others, underwent atrophy after hypophysectomy. No statement was made at that time with regard to the question of parathyroid repair after hypophyseal replacement therapy by transplantation. Schour and Van Dyke (8) described shrinkage of epiphyseal cartilages and gradual obliteration of the pulp cavities of the incisors by dentin, as a result of hypophysectomy in the rat (1931).

Evans, in a recent review of anterior pituitary function (9) summarized the situation with regard to the parathyroid as follows: "There seems to be no question but that we have to do with a disturbance of calcium



A B

Figure 4. Photomicrograph of a normal human parathyroid gland (x 400). B—Photomicograph of the parathyroid gland of Dr. Cushing's case of pituitary basophilism (x 400).

metabolism after hypophysectomy as reflected in the decreased calcium content in the blood; (no data or reference given) whether this is due to the correlated subnormality of the parathyroid glands remains to be established. Changes in the parathyroids as a result of hypophysectomy have not been adequately studied as yet. It is difficult to view the cessation of growth of the skeletal system after hypophysectomy as essentially due to disturbance in the inorganic salt metabolism; it is more justifiable to refer it to a singular failure in cartilage proliferation in the epiphyseal discs and, of course, the dwarfism is participated in by all the organs and tissues of the body."

Our present study indicates that in the intact rabbit, histological evidences of hyperplasia and overactivity of the parathyroids can be induced

by injection of emulsions or extracts of the anterior pituitary of beef. Whether this effect of such substances is an independent one and separate from the other known anterior pituitary effects or "hormones," such as Prolan A-B complex, thyreotropic or the crude growth extract of Evans, will be of considerable interest. That it may be an independent effect is indicated by the following points in our protocols. It was noted that animals 710, 712, 715 and 716 had resting ovaries, but showed definite parathyroid hyperplasia. Likewise, rabbits 265, 219, 226, 214 and 251 showed positive parathyreotropic effects when treated with pregnancy urine with no demonstrable effect in their thyroid glands Pregnancy urine has been repeatedly investigated and found negative for thyreotropic effect by several authors (10). It can be argued, therefore, that the parathyreotropic effect is at least separate from the gonadotropic and thyreotropic effects. Its independence from Evan's purified growth hormone is less clearly amenable to proof since it is conceivable that the skeletal growth obtained by pituitary products depends on the stimulation of epiphyseal cartilage growth and calcification, two phenomena intimately bound up with parathyroid activity.

To prove that the histological evidences which we have adduced in favor of a parathyreotropic effect of the anterior pituitary have functional significance, we are now engaged in metabolic studies of calcium, phosphorus and phosphatase in dogs subjected to treatment with our pituitary extracts. An anatomical study of the structure of the bones and epiphyseal cartilages of animals subjected to pituitary extract treatment is also under way.

SUMMARY AND CONCLUSIONS

In a series of seven experiments, the parathyroid glands of 48 rabbits subjected to injections of anterior lobe extracts and of pregnancy urine, as well as of several proprietary preparations from these sources, were grossly and microscopically compared with those of 17 reference control animals. The latter received either no injections or were given injections of heated pituitary tissue, normal urine, or emulsions of fresh brain substance of cows.

It was found that those animals which had been treated with unheated pituitary products and extracts of pregnancy urine exhibited parathyroids which were, as a rule, grossly larger and more vascular than those of the control group. They showed histological changes consistent with hypertrophy and hyperplasia. The criteria for the latter were described by Erdheim for the rat and were found remarkably applicable to the rabbit. Photomicrographs, drawings and measurements of representative normal and hyperplastic glands are presented to illustrate the type of changes encountered.

The degree to which these changes occurred in the individual animals varied according to the dosage and duration of treatment.

Control animals showed minor or no changes from normal in the gross and microscopic structure of their parathyroid glands.

The authors wish to express their thanks to Dr. J. H. Means, Dr. Harvey Cushing, Dr. Fuller Albright, Dr. Walter Bauer and Dr. Tracy B. Mallory for advice and help in the completion of this study.

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After the completion of the manuscript for this report and following its public presentation before the Harvard Biological Society (November 18, 1933) and the Harvard Medical Society (December 12, 1933) (see report of latter meeting in New England Medical Journal), there appeared a short report in the December 16, 1933, issue of the Klinische Wochenschrift (Vol. 12; No. 50; p. 1944) entitled: "Parathyreotrope Wirkung von Hypophysenvorderlappenextracten." We are pleased to call attention to it.

STUDIES OF THE ADRENAL GLANDS IN HEALTH AND DISEASE

II. EFFECTS OF AN EXCESS OF CORTICAL HORMONE IN ADDISON'S DISEASE

JACOB KINCOV, M.D.
Easton Hospital
EASTON, PA.
FREDERICK O. ZILLESSEN, M.D.
Easton Hospital
EASTON, PA.
AND
LEONARD G. ROWNTREE, M.D.
Philadelphia Institute for Medical Research
PHILADELPHIA, PA.

The following case history is of unusual interest because of the tremendous amounts of cortical hormone employed. The object of using these large doses was to ascertain whether or not larger amounts of the cortical hormone would markedly affect the level of the blood pressure. We were also interested to determine how long after the administration of excessive amounts the symptoms of Addison's disease would remain in abeyance. The cortical hormone employed was prepared by Swingle and Pfiffner and was of unusual potency, 80 dog units per cc.* Doses of 60 cc. were administered intravenously on three successive days. Thus we had the opportunity to determine both the immediate and later effects of repeated doses of 4800 dog units in a case of Addison's disease.

Case History. Mrs. J. P., aged 46, American, white, female, was admitted to the Easton Hospital on November 22, 1932, complaining of loss of weight, marked progressive weakness, and a brownish pigmentation of the skin. She stated that she had been well up to May, 1932, at which time she began to notice that she tired very easily, and that her skin was becoming "tan" in spite of her indoor occupation. This weakness progressed until by July she was forced to stop work. At about the same time she had become quite bronzed. She noticed that she had begun to lose weight, but attributed this to a strict but meager diet which had been prescribed for her by a physician. Aside from constipation which had been chronic for years, she had no gastro-intestinal symptoms. On the date of admission she weighed 149 pounds; in May she had weighed 210 pounds. Except for the usual childhood illnesses, her past history was essentially irrelevant.

The most striking thing about her physical examination at the time of her admission was the very pronounced pigmentation. This was of a tannish brown color, involving the entire body, but was more pronounced over the exposed parts and at the creases. The gums and mucous membrane of the mouth showed a patchy bluish black pigmentation. She showed evidence of a rapid loss of weight, but was still well padded with fat. Her blood pressure was systolic 110, diastolic 80. A diagnosis of Addison's disease was made.

Clinical Course. The patient was kept in bed and had no complaints except for her weakness. Her appetite was fair. There was no special therapy. About two weeks after admission on December 4, 1932, she began to complain of mild nausea. This was the first symptom of what eventually became a typical adrenal crisis. Within a few days her nausea had become so pronounced that she refused even water. She had no desire for food and vomited constantly. Her blood

*For the cortical hormone used we are indebted to Drs. Swingle and Pfiffner and to the Josiah Macy, Jr., Foundation.

pressure fell to about 84 systolic and 60 diastolic. Her skin became dry and she developed a mild acidosis. Hiccough, which was not very severe, occurred and persisted for several days. The patient became very listless and slept the greater part of the time. Her pigmentation became more intense. During this crisis the patient was given a daily intravenous injection of 10 per cent glucose in saline with only slight effect. The anorexia and vomiting became less pronounced and the hiccough ceased, but the extreme nausea persisted. On December 13, 1932, treatment with Eschatin, Swingle and Pfiffner's cortical hormone, generously supplied by them, was begun. For a few days several small doses of 5 to 10 cc. were given by vein with scarcely any effect on the general symptomatology. It was decided at this point to try large doses and note whether the adrenal crisis could thus be overcome. However, it was necessary to delay this for several days until a sufficient supply of Eschatin could be procured. On December 22, 1932, intensive treatment was begun. Sixty cc. was given intravenously. Towards the end of the injection the patient experienced slight pain in the epigastrium and over the precordium which lasted for only a few moments. She reported "a taste of garlic" after only a few cc. had entered the vein. Her blood pressure rose almost immediately to about 130/90 but dropped to 96/70 within two hours. The next morning her nausea had disappeared. She ate the largest breakfast since

Figure 1. Drawing of patient showing pigmentation.

the onset of the adrenal crisis. She stopped vomiting. On the next two days similar doses were given. The result was remarkable. Her appetite improved from the start. Her mental attitude changed; she became jovial and happy. She began to regain strength rapidly and on the 7th day after the first injection she was allowed out of bed and soon began to walk about. She began to gain weight slowly and continued in good condition until on January 15, 1933, we allowed her to go home. There had been no change in her blood pressure and only slight, if any, variation in her pigmentation. No further Eschatin was given because we desired to see how long the patient would continue well.

Following her discharge she was seen several times in the Out-Patient Department and reported that she felt fairly strong and had no return of symptoms. However, on February 3, 1933, forty-two days after her last dose of Eschatin, it was found necessary to readmit her because of a beginning onset of weakness which she admitted with reluctance. She had lost the alertness, cheerfulness, and vigor which she showed after the original injection. Her appetite was poorer but nausea had not yet returned.

It was decided at this point to determine whether the patient would not respond to small doses of Eschatin given hypodermically. Two cc. were given

daily for four days. The patient showed no response and her condition became critical. All the old symptoms returned, the weakness, nausea, vomiting and anorexia. All were very pronounced. At the same time daily intravenous injections of 10 per cent glucose in saline were given. We were finally forced to resort again to large doses of Eschatin and four successive daily injections of 40 cc. each were given by vein. At this point the patient improved slightly. However, the improvement was very disappointing when compared with the response obtained at the beginning of her treatment.

The subsequent course was gradually downward. Further attempts to overcome the cortical deficiency with smaller doses of Eschatin intravenously were unavailing. She ran a moderate low grade fever, became extremely dehydrated in spite of fluids by vein and by hypodermoclysis and on March 18, 1933, she died.

Protocol. An autopsy was performed five hours post-mortem on a white female, aged 46 years, height 155 cm., weight 130 lbs. Permission was limited to the thorax and abdomen. The skin appeared to be normally elastic. There was a generalized bronzing which was markedly accentuated over the face, neck, sternal region, nipple aroela, knees, anticubital fossae, "garter areas," extensor surfaces of arms and all the folds of the skin. Over these areas there were several, irregularly distributed, small, deeply pigmented areas resembling black freckles, and measuring from 1 to 3 mm. in diameter. One such freckle was

Figure 2. Right adrenal, longitudinal section showing caseous areas (centimeter scale).

found on the posterior surfaces of both ears. The hair was gray and somewhat dry. The mucous membrane of the mouth presented a bluish-brown pigmentation.

On opening the thoracic cavity numerous fibrous adhesions were seen to obliterate completely the left pleural sac. A few such adhesions were found in the right sac. At the apices of both lungs a slight amount of scarring was present. Both lower lobes contained an increased amount of fluid. The lymph nodes at the hilus of both lungs were somewhat enlarged and contained small caseated nodules which on section showed an active tuberculosis. The heart was normal. The thymus was replaced by fat. The thyroid gland was normal except for a small colloid adenoma, about 0.5 cm. in diameter, in the right lower pole.

On opening the peritoneal cavity, thick fibrous peri-splenic and peri-hepatic adhesions were found to be present. There were many thick fibrous bands connecting the gall-bladder and colon. The mesentery contained several small, calcified nodules. The spleen weighed 485 grams. It was dark red in color and irregularly distributed throughout the spleen were several small, hard, white nodules, averaging about 3 cm. in diameter. The center of these nodules consisted of caseous material. Sections showed an active tuberculosis. In the right lobe of the liver were several small, round, red areas, well circumscribed and measuring from 0.3 to 1.0 cm. in diameter. These areas were soft and on section were seen

to consist of dilated spaces filled with blood. In the anterior portion of the right lobe was a calcified mass measuring 0.5 cm. in diameter. At the head of the pancreas was a lymph node measuring 4x2 cm., firm and on cut section presenting a white, nodular appearance. A smaller adjacent node had a similar appearance. Microscopic sections from both nodes showed an active tuberculosis.

The right suprarenal weighed 40 grams and measured 8x5x2 cm. The periadrenal tissue was closely adherent to the gland and the consistency of the tissue was greatly increased. The cut surface presented a mottled yellowish-white appearance showing irregular strands of white tissue and varying sized yellowish areas containing caseous material. Several of the areas contained calcareous material. It was impossible to distinguish any normal suprarenal tissue grossly and the central vein was not seen. The left suprarenal weighed 28 grams and measured 8x3x1.5 cm. The periadrenal tissue was adherent and the gland was firm and increased in consistency. The cut section was the same as that of the right adrenal except that certain areas could be identified as containing glandular elements. Microscopic sections from the suprarenal glands showed a widespread

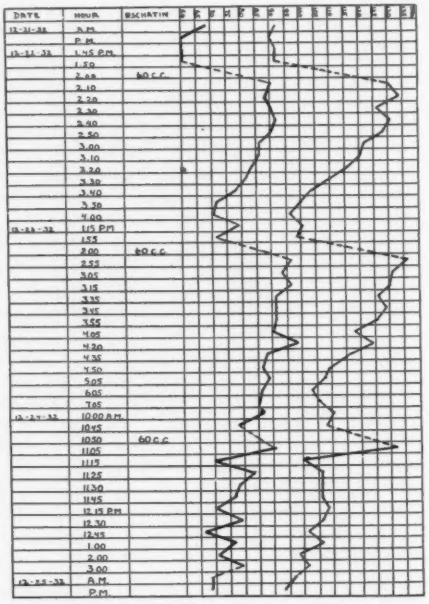

Figure 3. Graph showing effect of injection of cortical extract on blood pressure.

active tuberculosis with a moderate fibroblastic reaction. In some areas cortical cells were present. They were large, had a pale staining nucleus, and a finely granular cytoplasm. In none of the sections examined could medullary tissue be found. Sections were stained for acid-fast micro-organisms but they could not be demonstrated.

The Pathological Diagnosis was fibrocaseous tuberculosis of the suprarenal glands (Addison's disease); fibrocaseous tuberculosis of the spleen with perisplenitis; fibrocaseous tuberculosis of the pancreas; healed tuberculosis of the liver with chronic perihepatitis and cholecystitis; a cavernous hemangioma of the liver; healed tuberculosis of the mesenteric nodes; healed tuberculosis of the pulmonary apices with edema and congestion; and chronic bilateral fibrous pleurisy.

This represents a typical case of Addison's disease of 10 months' duration. Pigmentation was marked; there was profound weakness; the weight

loss was excessive (80 pounds); the gastro-intestinal manifestations—nausea, vomiting and anorexia were of the usual type. This patient also showed shadows suggestive of calcification in the adrenal by roentgenography. The patient responded rapidly and markedly to huge doses of the cortical hormone, left the hospital and remained almost perfectly well for a period of some weeks. Treatment with small doses of the cortical hormone subsequent to the recurrence of the manifestations of the disease was ineffective; large doses were relatively so. The clinical picture during the terminal days was febrile in nature. Active tuberculosis probably played some rôle in the death. At autopsy the destruction of the adrenal glands by tuberculosis was verified as well as was the presence of tuberculosis elsewhere in the body. The glands were of unusual size, 28 and 40 grams, respectively.

No untoward symptoms were observed following the intravenous use of 4800 dog units of the cortical hormone on three successive days. The immediate effects on blood pressure were marked but transient. The more prolonged effects were evidenced by the higher level of both the systolic and diastolic pressures on each successive day, 110 mm. Hg. systolic on the third day as compared with 93 mm. Hg. on the first day. Symptomatic recovery was almost complete for a period of more than a month. When used subsequently in large doses the cortical hormone was relatively ineffective.

Several interesting questions present themselves. (1) Is the transient increase in blood pressure indicated in these charts due to the effect of cortical hormone or to retained or unremoved epinephrine? According to Dr. Swingle, the product used contained 0.001 mg. of epinephrine per cc. and the amount of epinephrine per injection was between 0.6 and 1.2 mg. The early rise in blood pressure might be due in part to epinephrine but the later effects more propably to changes in the blood volume.

(2) Did excessive amounts of the cortical hormone administered render the organism relatively unresponsive to subsequent amounts? The answer is not apparent. However, the fact that subsequent treatment with the hormone was relatively ineffectual is interesting and worthy of record.

(3) What is the fate of these large amounts of cortical hormone after their administration? In this patient an investigation of the urine and blood from the standpoint of the presence or absence of this hormone after the administration of large amounts was planned but unfortunately not carried out. However, in similar studies in animals Dr. Swingle reports that the cortical hormone is never found in the urine except in traces.

(4) To what was death due in this patient? The patient died despite the known presence in the body of amounts of cortical hormone ordinarily sufficient. Either because of insusceptibility of the organism or irreversible damage which resulted from hormonal imbalance, the organism failed to react to this hormone. Perhaps some other entirely different factor was at work. The amount of tuberculosis present seems hardly sufficient in itself

to cause death; yet, in one whose general resistance to infection was so greatly lowered, tuberculosis may have played an important part.

SUMMARY

A patient with Addison's disease was treated with unusually large doses of the cortical hormone of the adrenal gland isolated by Swingle and Pfiffner, 5000 dog units daily for three successive days. The immediate results were excellent. Without further treatment the patient left the hospital and remained in perfect health for a period of six to seven weeks. Subsequent treatment was relatively ineffective. The patient died, necropsy revealing destruction of the adrenals by tuberculosis and also rather widely disseminated tuberculosis.

WEIGHT CHANGES IN THE SUPRARENAL GLANDS OF ALBINO RATS ON VITAMIN E DEFICIENT AND FAT DEFICIENT DIETS*

CHARLES M. BLUMENFELD
Department of Anatomy, University of Utah
SALT LAKE CITY

Past and present work indicates associations of the suprarenal glands with numerous and varied activities of the body. Possible relations to metabolism may be indicated by morphologic changes in these glands resulting from dietary alterations. This investigation includes studies of the effects of vitamin E deficiency and fat deficiency.

MATERIALS AND METHODS

The suprarenal glands studied were obtained from 35 male and 141 female rats distributed between the experiments as follows: vitamin E deficiency, 91 female Wistar albino rats; fat deficiency, 22 male and 46 female Wistar albino rats.† An additional experiment, to be explained shortly, involved the use of 13 male and 4 female Wistar albino rats.

In the vitamin E deficiency experiment several rats were kept in each cage, fed the basal diet from a common food pan and supplied with tap water from a siphon type container. The animals were placed in four groups: a virgin control group of 22 female rats never placed with a male; a pregnant control group of 22 female rats killed on various days of a first pregnancy; a test group of 23 female rats fed on an E deficient diet from weaning to autopsy on various days of a second pregnancy; and a "cured" group of 24 female rats reared on an E deficient diet from weaning through a first pregnancy, then placed on a diet containing vitamin E and killed on various days of a second pregnancy. The virgin and pregnant control groups were given the following diet:

Whole ground wheat	67.5 per cent
Casein (commercial)	15.0 per cent
Whole milk powder	10.0 per cent
Calcium carbonate	1.5 per cent
Sodium chloride	0.8 per cent
Butter (unsalted)	5.2 per cent

To 3000 grams of this mixture 30 grams of cod liver oil were added to

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†The care and management of certain groups of the vitamin E deficiency experiment (test and "cured") were under the direction of Dr. J. A. Urner. The fat deficiency experiment was conducted by Dr. and Mrs. G. O. Burr. To them I wish to express my thanks for much of the material obtained.

insure adequate amounts of vitamins A and D. The test and "cured" rats were given the following basal diet:

Sucrose (commercial)	45.0 per cent
Casein (commercial)	30.0 per cent
Lard	20.0 per cent
McCollum's salt mixture 185	4.5 per cent

In addition test and "cured" rats each received daily 0.6 gram powdered yeast and 3 drops cod liver oil. After the first pregnancy the "cured" group was given 0.2 gram yeast and 0.4 gram wheat germ (source of vitamin E) instead of 0.6 gram yeast.

The fat deficiency experiment included 10 male and 11 female rats as controls, 6 male and 17 female rats as tests and 6 male and 18 female rats as "cured" animals. Control rats received a diet of varying proportions of pure casein, sucrose, McCollum's salt mixture No. 185 and lard (for details consult the paper of Burr and Burr, 1929), plus a daily accessory of 0.7 gram ether-extracted yeast and the non-saponifiable matter from 0.5 gram cod liver oil per week. Test rats were given a similar diet except that no lard was included. The "cured" group consisted of test rats cured of the symptoms of fat deficiency by addition to the diet of one of the following: corn oil, poppy seed oil, lard, butter, methyl oleate, methyl linoleate, linseed oil, linoleic acid, methyl arachidonate and various other substances.

The technic of autopsy was similar to that described by Freudenberger (1932). The suprarenals were fixed in 10 per cent unneutralized formalin, Zenker's fluid or Helly's fluid. One gland from each pair was imbedded in paraffin and cut at 5 or 10 microns thickness. Every twentieth of the sections cut 5 microns thick and every tenth of the sections cut 10 microns thick was mounted and stained with Harris' hematoxylin and eosin, so that each gland was finally represented by a series of sections taken at 100 micron intervals.

The object of this study being the determination of changes in size of the whole suprarenal, cortex and medulla, the paper outline method originated by Hammar (1914) and modified by Jackson (1917) was found to be best. Using a Leitz-Edinger projection apparatus, the cortex and medulla of the suprarenal sections taken at 100 micron intervals were outlined on "Artesian Linen Record" paper at a magnification of 33 diameters. The drawings were cut out and cortical and medullary portions weighed separately. The paper weight proportion of cortex to medulla was considered to represent the actual proportion. It is realized that shrinkage on fixation, differences in specific gravity, condition of vascular supply to the gland and other factors make these calculations approximate, but as yet no more accurate method applicable to rat suprarenals has been devised. By applying the proportion of cortex to medulla as calcu-

lated from paper weights to the weight of the glands as determined at autopsy, weight of cortex and of medulla was obtained.

In using this method with a large number of glands it was of great practical importance to determine at what interval sections should be taken to be outlined. Jackson (1919), in his study of the cortico-medullary proportions of the suprarenal glands of rats, drew sections at intervals of such a magnitude that about 50 drawings per gland resulted. Sun (1929) claimed that every section must be drawn to obtain accurate results.

To settle this problem the suprarenals of 13 normal adult male Wistar albino rats, similarly fixed, sectioned at 5 microns thickness and mounted serially, and the suprarenals from 4 normal adult female Wistar albinos, similarly fixed, sectioned at 10 microns and mounted serially, were employed. Every third section of the male glands was outlined, so that each

TABLE I

STATISTICAL COMPARISON OF CORTICO-MEDULLARY RATIOS OBTAINED BY DRAWING SECTIONS AT VARIOUS INTERVALS

Section Interval, Microns	Mean	Standard Deviation	Coefficient of Variation	Difference	Standard Error	Significance Ratio
			Male Group (13)			
15	9.969	2.228	22.345			
30	10.000	2.283	22.825	−0.031	0.651	0.05
60	10.069	2.377	23.608	−0.100	0.655	0.15
120	10.146	2.359	23.253	−0.177	0.662	0.27
240	9.938	2.456	24.710	0.031	0.677	0.05
			Female Group (4)			
10	13.050	0.814	6.241			
20	13.025	0.854	6.556	0.025	0.590	0.04
30	13.025	0.854	6.556	0.025	0.590	0.04
60	13.025	0.907	6.963	0.025	0.609	0.04
120	12.975	1.072	8.262	0.075	0.691	0.11
240	12.825	1.440	8.922	0.225	0.702	0.32

drawing represented 15 microns of gland. In Sun's material every section, cut at 10 microns, was drawn. For this reason every section of the female gland was drawn. The drawings were numbered, then cut out, separated and weighed in such groups that calculations of cortico-medullary proportions were obtained from drawings of sections at 15, 30, 60, 120 and 240 micron intervals in the male glands; and at 10, 20, 30, 60, 120 and 240 micron intervals in the female glands. Cortico-medullary ratio was determined solely as a matter of convenience because this expression of cortex size in terms of medulla as one has only one term to be considered and is affected by small degrees of change in the size of cortex or medulla.

In Table I the results show that it makes no significant difference whether the sections drawn are taken at 10 or 240 micron intervals. However, the results for individual glands do become more variable the greater the interval between sections drawn as shown by the coefficient of variation

TABLE II

Statistical Data for All Measurements

	Age, Days	Body Weight, gms.	Body Length, mms.	Suprerenal Weight, mgms.	Cortex Weight, mgms.	Medulla Weight, mgms.
VITAMIN E DEFICIENCY EXPERIMENT						
Virgin Control Group						
Mean	107.273	185.818	199.818	43.509	40.500	3.000
Standard deviation	25.778	4.261	2.970	4.899	4.899	0.480
Probable error	3.794	0.627	0.437	0.721	0.721	0.071
Pregnant Control Group						
Mean	117.364	200.955	201.545	44.901	41.059	3.032
Standard deviation	17.434	19.824	4.195	4.690	4.583	0.520
Probable error	2.566	2.918	0.617	0.690	0.675	0.076
Vitamin E Deficient Group						
Mean	155.087	223.000	201.913	47.557	44.839	2.717
Standard deviation	24.676	21.845	9.816	8.426	7.937	0.648
Probable error	3.548	3.141	1.412	1.211	1.141	0.093
"Cured" Group						
Mean	154.333	236.292	204.208	54.900	51.800	3.100
Standard deviation	19.048	29.036	2.511	8.718	8.246	0.700
Probable error	2.679	4.084	0.353	1.226	1.159	0.098
FAT DEFICIENCY EXPERIMENT						
Female Control Group						
Mean	545.455	200.545	205.727	53.082	47.336	5.745
Standard deviation	89.635	39.861	7.669	8.367	7.937	1.446
Probable error	19.119	8.502	1.636	1.785	1.693	0.308
Female Test Group						
Mean	340.278	166.111	195.000	45.082	41.418	3.664
Standard deviation	115.269	30.957	7.599	9.487	9.110	0.640
Probable error	18.857	5.064	1.281	1.600	1.537	0.108
Female "Cured" Group						
Mean	342.500	196.500	208.222	43.544	38.939	4.606
Standard deviation	106.516	22.812	5.621	6.928	6.557	0.911
Probable error	17.425	3.732	0.920	1.133	1.072	0.149
Male Control Group						
Mean	316.400	281.700	226.100	30.760	27.010	3.750
Standard deviation	103.080	17.378	3.635	3.903	3.148	1.054
Male Test Group						
Mean	172.172	182.172	207.000	28.183	25.567	2.617
Standard deviation	80.221	46.387	20.327	5.837	3.841	0.662
Male "Cured" Group						
Mean	310.333	270.833	227.000	28.350	24.117	4.233
Standard deviation	21.620	47.086	10.276	5.926	4.939	1.360

values. For this reason an interval of 100 microns between sections was used.

In most quantitative studies the conclusiveness of the results is partially dependent on the number of individuals in the sample used. Therefore, it is advantageous in a study such as the one here presented to make use of as large a number of individuals as the material available and the methods employed allow. Since the above experiment on the number of sections to be drawn reveals no objections to drawing far less than every section, and since the time and labor saved by drawing sections at 100 instead of 10 micron intervals can be well employed in studying a larger number of glands, this procedure has been adopted.

In the statistical analysis of the data formulae modified for small samples were employed. The corrections involved are based mainly on the methods of Fisher (1930). To determine the significance of differences between mean values for groups of 15 or more individuals the significance ratio was calculated, interpretation of it being obtained from Pearl (1930), Table A, Appendix III, page 438. For samples of less than 15 individuals a different set of formulae were used, the significance ratio thus obtained being interpreted from Table IV at the end of Fisher's book (1930). In Tables II and III, where the statistical data for these experiments are recorded, the values for the male groups of the fat deficiency experiment were derived by formulae most suitable for groups of less than 15 individuals. Therefore, in Table II the probable error of the mean is not given for these groups, because it is not made use of in deriving the significance ratio. The term P, in Table III, represents the significance ratio, but the P of the male groups differs from that of the others. When the type of P calculated for the larger groups is 3.0 or more, the difference between means is considered significant, there being less than one chance out of 20 that the observed difference is accidental, due to random sampling. For the smaller male groups a P of 0.05 to 0.02 or less is considered to indicate significance for the same reason.

The similarity of stage of physical development is of highest importance in comparing organ weights of different groups of animals. To decide what criteria are best for determining such similarity, a study was made on 41 normal female Wistar albino rats (controls from various experiments) as to the correlation between suprarenal weight and three common measurements: age, body weight and body length. The correlation ratios obtained were: suprarenal weight with age, 0.28; with body weight, 0.69; with body length, 0.67. Obviously body weight and body length are the more important criteria.

RESULTS

(The figures quoted are means. All other statistical data appear in Tables II and III.)

1. *Vitamin E Deficiency Experiment*

a. General Results. The general results of this experiment are presented in full by Urner (1931). The rats were normal as to growth, oestrus rhythm and breeding behavior. Embryonic death and resorption occurred

TABLE III

DIFFERENCES BETWEEN MEANS AND THEIR SIGNIFICANCE

Groups Compared		Age	Body Weight	Body Length	Suprarenal Weight	Cortex Weight	Medulla Weight
VITAMIN E DEFICIENCY EXPERIMENT							
Virgin control with Pregnant control	Diff.	−10.091	−15.136	−1.737	−0.582	−0.559	−0.032
	P. E.	4.580	2.985	0.760	0.993	0.988	0.104
	P.	2.4	5.1	2.3	0.6	0.6	0.3
Virgin control with E deficient	Diff.	−47.814	−39.182	−2.095	−4.048	−4.339	0.283
	P. E.	5.195	3.203	1.480	1.409	1.350	0.117
	P.	9.2	12.2	1.4	2.9	3.2	2.4
Virgin control with "Cured"	Diff.	−47.061	−50.473	−4.390	−11.391	−11.300	−0.100
	P. E.	4.645	4.132	0.560	1.422	1.365	0.121
	P.	10.1	12.2	7.8	8.0	8.3	0.8
Pregnant control with E deficient	Diff.	−37.723	−24.045	−0.368	−3.466	−3.780	0.315
	P. E.	4.379	4.287	1.540	1.394	1.326	0.120
	P.	8.6	5.6	0.2	2.5	2.9	2.6
Pregnant control with "Cured"	Diff.	−36.970	−35.337	−2.663	−10.089	−10.741	−0.068
	P. E.	3.710	5.019	0.710	1.407	1.341	0.124
	P.	9.9	7.0	3.8	7.7	8.0	0.6
E deficient with "Cured"	Diff.	0.754	−11.292	−2.295	−7.343	−6.961	−0.383
	P. E.	4.446	5.152	1.460	1.723	1.626	0.135
	P.	0.2	2.2	1.6	4.3	4.3	2.9
FAT DEFICIENCY EXPERIMENT							
Female Groups							
Control with Test	Diff.	217.219	31.545	10.727	8.000	5.918	2.080
	P. E.	26.870	9.820	2.130	2.397	2.287	0.326
	P.	8.1	3.2	5.0	3.3	2.6	3.9
Control with "Cured"	Diff.	205.955	4.045	2.495	9.538	8.397	1.139
	P. E.	19.213	9.285	1.890	2.114	2.004	0.342
	P.	10.7	0.4	1.3	4.5	4.2	3.3
Test with "Cured"	Diff.	−11.265	−27.500	13.222	1.538	2.479	−0.941
	P. E.	25.693	6.170	1.650	1.961	1.874	0.184
	P.	0.4	4.5	8.0	0.8	1.3	5.1
Male Groups							
Control with Test	Diff.	144.228	99.528	19.100	2.577	1.443	1.133
	S. E.	49.343	16.023	6.452	1.988	1.763	0.482
	P.	.01	.02–.01	.01	.3–.2	.5–.4	.05–.02
Control with "Cured"	Diff.	6.067	10.867	−0.900	2.410	2.890	−0.480
	S. E.	43.192	16.213	3.510	2.440	2.006	0.606
	P.	.9–.8	.6–.5	.9–.8	.4–.3	.2–.1	.5–.4
Test with "Cured"	Diff.	−138.161	−88.661	−20.000	−0.167	1.447	−1.613
	S. E.	33.917	26.983	9.298	3.396	2.555	0.615
	P.	.01	.01	.1–.05	.4–.3	.6–.5	.05–.02

Diff.—Difference. P. E.—Probable error of difference. S. E.—Standard error of difference. P.—Significance ratio.

in all rats deprived of vitamin E. Some normal and some abnormal placentations occurred in the "cured" group. Microscopic examination showed that embryonic death was preceded by rarefaction of the mesenchyme and failure of the blood-forming tissues. Since the suprarenal cortex

seems to be linked up somehow with the endocrine-reproductive complex, the possible changes in the suprarenal gland during E deficiency are of interest.

b. Comparability of Groups. Data given in Tables II and III show the virgin control, pregnant control and E deficient groups to be essentially similar in body length. The "cured" group has a body length significantly greater than that of the control groups, but not of the E deficient group. Body weight cannot be used as a criterion, some of the rats being pregnant. The test groups are 32 to 45 per cent older than the control

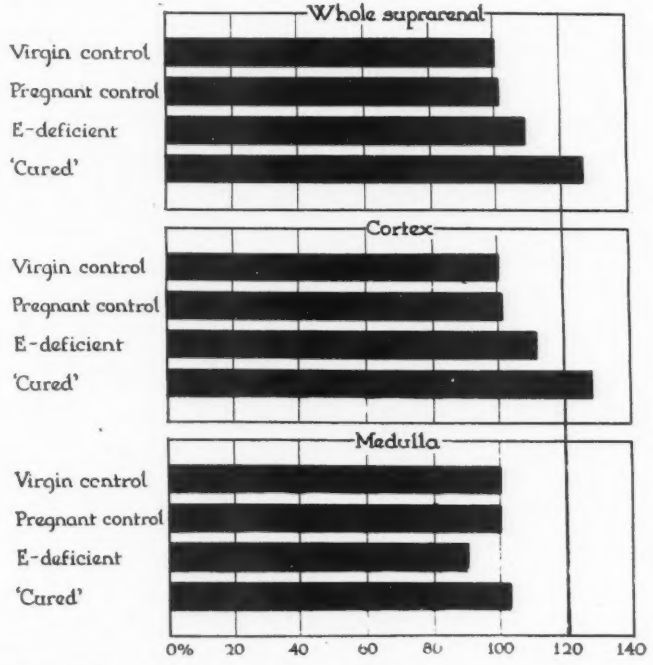

Figure 1. Weights of whole suprarenal, cortex and medulla of various groups in the E deficiency experiment expressed as per cent of the virgin control group weights.

groups, but, as shown by the correlation ratios, this matters little when body length or body weight are similar.

c. Weight of Whole Suprarenal, Cortex and Medulla. The mean whole suprarenal weights, in milligrams, for the various groups are: virgin control, 43.5; pregnant control, 44.1; E. deficient, 47.6; "cured," 54.9. Considering the whole suprarenal weight of the virgin control group as 100 per cent, the weights of the other groups expressed as per cent of the virgin control group are: pregnant control group, 101; E deficient, 109; "cured," 126. Figure 1 shows these relations.

The only significant difference is that between the "cured" group and all other groups. With respect to the control groups the greater length of the "cured" group may account for part of the difference in whole suprarenal weight, but the E deficient group being highly similar to the "cured" group in age, weight and length, the difference between these two groups is of unquestionable importance.

A study of the weight of cortex and medulla serves to explain the whole suprarenal weight changes. The average cortical weights, in milligrams, for the various groups are: virgin control, 40.5; pregnant control, 41.1; E deficient, 44.8; "cured," 51.8. Virgin and pregnant control groups are practically alike. The significance ratio for the difference between E deficient and virgin control groups is 3.2, between E deficient and pregnant control groups, 2.9. Although bordering on statistical significance, the much greater age of the E deficient group may make the difference of doubtful importance. The cortex of the "cured" group is unquestionably hypertrophied, no matter with what group the comparison be made. Expressed as per cent of the virgin control cortex weight that of the pregnant control group is 101; E deficient, 111 and "cured," 128. The relations are practically the same as for whole suprarenal weight (Fig. 1).

Medulla weights in milligrams are: virgin control, 3.0; pregnant control, 3.0; E deficient, 2.7; "cured," 3.1. A surprising difference is the lighter weight of the E deficient medulla. Judging from the significance ratio the difference is of questionable importance; but if the greater length and possibly the greater age of the E deficient group is used to explain the occurrence of a heavier cortex, it cannot at the same time explain a lighter medulla. On the contrary, it increases the importance of this finding. The medullary weights of the control and "cured" groups are practically alike. Figure 1, which portrays these relations, shows clearly the drop in medullary weight in the group deprived of vitamin E, and the recovery from this decrease in the group refed vitamin E.

A summary of the findings as to whole suprarenal, cortical and medullary weights brings out the following points: A single pregnancy in normal Wistar albino rats produces no changes in the weight of cortex or medulla. This agrees with the work of J. C. Donaldson (1924, 1928), and Anderson and Kennedy (1933), who also found no changes, but disagrees with the findings of Herring (1920). However, Herring's observations were not based on accurate studies. Anderson and Kennedy present an extensive survey of the literature to conclude that there is little evidence in favor of the rather common text book statement that the suprarenals hypertrophy during pregnancy. So-called hyperfunctional changes in the cortex of the suprarenals of rats deprived of vitamin E were reported by Bisceglie (1928). If increase in weight can be interpreted as evidence of hyperfunction, then there is an indication of such a change in my E deficient group, although the increase in weight over the control groups is of questionable significance. The medulla of the E deficient rat apparently under-

goes atrophy, from which refeeding vitamin E causes a recovery. The cortex of the "cured" group is definitely hypertrophied. Whether or not these changes are due to vitamin E deficiency alone, or the combined effect of vitamin E deficiency and pregnancy cannot be said; their confirmation awaits the results of similar experiments. Interpretation of these changes may be facilitated by a study of other organs affected by this deficiency.

2. *Fat Deficiency Experiment*

a. General Results. A discussion of the general results of this experiment appears in the papers of Burr and Burr (1929, 1930), from which the following essential points have been taken. Rats on a fat-free diet stop growing when they have attained 70 per cent (males) or 80 per cent (females) of the weight of their controls. Males then lose weight rapidly and begin to die; females lose weight less rapidly. Scaliness, inflammation, hemorrhage and necrosis of the tail, scaliness of skin, redness and swelling of hind feet, dandruff, and loss of hair especially about face, back and throat, are prominent and constant symptoms. The next most constant finding was bloody urine. Borland and Jackson (1931) found calcification in cells of some renal tubules and in necrotic areas of renal medulla, the most characteristic renal lesion. Various fatty substances in the diet cured the symptoms of the disease, the essential constituent of nearly all being linoleic acid. Burr and Burr conclude that linoleic is an essential fatty acid, and promulgate the hypothesis "that warm blooded animals in general cannot synthesize appreciable quantities of linoleic acid."

Since their discovery by Ecker (1846) the large amount of lipoids in the suprarenal cortex has led to the theory of its association with fat metabolism. Therefore, the suprarenals of these animals were considered worthy of study.

b. Comparability of Groups

On account of the marked sex difference in the size of the suprarenals, the sexes must be considered separately.

Females. From data in Tables II and III it is evident that control and "cured" groups are essentially similar in body weight and body length while the test group is both lighter and shorter—an effect of the dietary deficiency. Both test and "cured" groups, almost identical as to age, are 38 per cent younger than the controls. This may possibly play a part in the suprarenal weight differences.

Males. The various groups bear the same relations to one another as the female groups, with the exception that only the test group is younger.

Male and female groups, on the basis of the important criteria of body length and body weight, are suitable material for suprarenal weight comparisons.

c. Weight of Whole Suprarenal, Cortex and Medulla

Females. Mean whole suprarenal weights, in milligrams, for the control, test and "cured" groups, respectively, are: 53.1, 45.1, 43.5. The test

and "cured" suprarenal weights are significantly less than those of the controls, but there is no significant difference between the weights of test and "cured" (Table III). It must be recalled, however, that the test animals are definitely shorter and lighter than either the control or "cured." If this difference is due entirely to maintenance on a fat-free diet, then the lighter suprarenal weight is of importance. To determine whether the suprarenal weight differences are merely an expression of body size differences, comparisons were made with data given by Donaldson (1924). The suprarenal weight of each of the rats of the three groups was compared with the suprarenal weight of a rat of similar body length, as given by Donaldson. The mean per cent difference was calculated, with these results: control suprarenals, 11.8 per cent lighter; test suprarenals, 13.4 per cent lighter; "cured" suprarenals, 31.7 per cent lighter. Tested statistically these deviations are significantly different from one another. Thus the suprarenals of the test animals are not only smaller than those of the controls, but are also lower in weight than the suprarenals of normal animals of similar body length, indicating that absolute as well as relative atrophy has occurred. The same data demonstrate that the suprarenals of the "cured" rats were not cured. Instead, these glands remained at the level to which they had been reduced by the absence of fat from the diet.

Expressed as per cent of the control suprarenal weight the test suprarenal weight is 85, the "cured," 82 (Fig. 2). This again demonstrates the similarity in weight of the test and "cured" suprarenals, and the decrease in size of both these groups with respect to the controls.

The mean cortical weights, in milligrams, for the control, test and "cured" groups are: 47.3, 41.4 and 38.9. The cortical weight of the "cured" group is definitely less than that of the control, but essentially similar to that of the test group. The cortical weight of the test group is questionably lower than the control value (Table III). Figure 2 represents the cortical weights as per cent of the control cortical weight, wherein the trend is seen to be similar to whole suprarenal weight.

Mean medullary weights, in milligrams, for control, test and "cured" groups, respectively, are: 5.7, 3.7 and 4.6. All differences are significant. As shown in Figure 2, the medullary weights in terms of control medullary weight, are 64 per cent for the test and 84 per cent for the "cured" group. Apparently the suprarenal medulla of rats on a fat-free diet undergoes an atrophy from which curing the rats of symptoms brings about a partial recovery.

Males. The values for whole suprarenal weight, cortex weight and medulla weight, given in Tables II and III, exhibit a trend similar to that of the female groups. Figure 2 presents the similarity graphically. None of the differences between values are significant, except those between medulla of tests and the other two groups. This may be due to a sex difference in the response to the diets, or, as is more likely, it is an expression of the small size of the male groups.

Male and female Wistar albino rats maintained on a fat-free diet cease to gain not only in weight, as shown by Burr and Burr, but also in length. There is a concomitant cessation in growth or atrophy of both cortex and medulla of the suprarenal. Whether it is cessation of growth or atrophy is

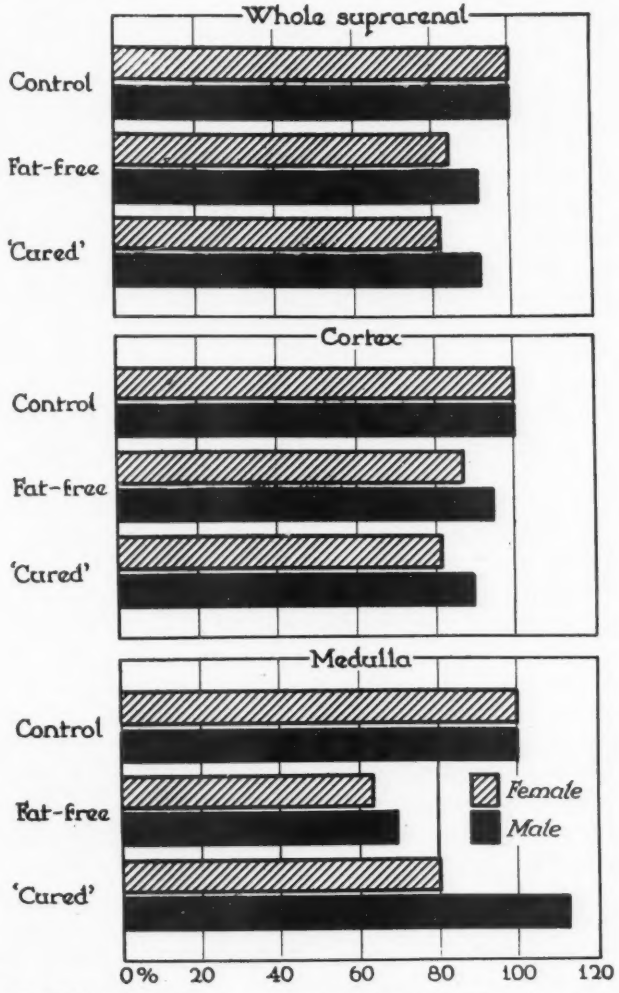

Figure 2. Weights of whole suprarenal, cortex and medulla of various groups in the fat deficiency experiment expressed as per cent of the control group weights.

difficult to decide because of inadequate control material, but judging from the whole suprarenal weight there is a small degree of absolute atrophy. This disagrees with the findings of Herter (1896), who fed young pigs on milk containing one three-hundredth part of fat and found the suprarenals

of these animals "appeared normal except for being unduly large." No other reports on this point were found in the available literature. Curing fat-deficient rats by feeding substances containing linoleic acid causes a renewal of growth of the medulla but not of the cortex, which remains at practically the same level to which it was reduced by the fat-free diet. The only finding statistically significant in both male and female groups is the atrophy and return to normal of the medulla. The similarity of cortical changes in both male and female groups, although statistically significant in the female group only, increases the importance of these observations. From these results it seems rather certain that the suprarenals are somehow linked with fat metabolism.

An interesting fact can incidentally be noted in Figure 2. In the male groups test and "cured" whole suprarenal weights are practically the same. A study of whole suprarenal weight alone would miss the true situation entirely. The cortex of the "cured" group is smaller than that of the test, but the marked and significant difference in medullary weights compensates for the difference in cortical weights, producing a false outward similarity in whole suprarenal weight. Therein lies the danger of grouping together two functionally different parts.

DISCUSSION

To the list of inexplicable suprarenal changes must be added the effects of vitamin E deficiency on the suprarenals of pregnant rats. My own study shows that a single pregnancy in healthy Wistar albino rats produces no change in the size of cortex or medulla. The rats used in the vitamin E deficiency experiment were pregnant twice, which introduces the possibility of the second pregnancy producing the changes found. The cortex of the E deficient rats was larger than that of the normal virgin or normal pregnant rats, the difference being on the borderline of statistical significance. The medulla of the tests weighs definitely less than the medulla of either of the control groups. The cortex of the "cured" group is heavier than the cortex of either of the control groups or the test group. The medulla of the "cured" group weighs practically the same as the virgin or pregnant control medulla, but is significantly heavier than the medulla of the E deficient group. Several hypothetical explanations, all of which may be tested by further experiments, can be advanced. Two successive pregnancies may cause an hypertrophy of the cortex. Since vitamin E deficiency interferes with the normal course of pregnancy it might retard, partially, this hypertrophy. "Curing" the rats by furnishing vitamin E would permit the hypertrophy to proceed, and the "cured" rats would thus have a cortex larger than that of either the test or control groups. The medullary change, consisting of a decrease in weight in E deficient pregnant rats and a return to normal when vitamin E is furnished, may be due to vitamin E deficiency alone or to the combination of E deficiency and pregnancy. Whatever the

true interpretation may be, these observations strengthen the theory of a relationship between the suprarenals and the reproductive system.

Male and female Wistar albino rats maintained on a fat-free diet are found to have a relative and probably an absolute atrophy of both cortex and medulla of the suprarenals. This may be a direct effect of the absence of fat from the diet or may be a part of the cessation of growth experienced by these animals. Some of the rats were also deficient in vitamin E, but since an hypertrophy of the cortex occurred in E deficient pregnant rats, either E deficiency alone has no effect on the suprarenals, or the effect of fat deficiency obscures the effect of E deficiency. However, the fact that the E deficient rats were normal as to growth before being mated, whereas the fat deficient rats stopped growing, makes it probable that the suprarenal atrophy was not due to the vitamin E deficiency. When the fat deficient rats are returned to normality, outwardly, by feeding various substances containing linoleic acid, the cortical weight remains unchanged while the medullary weight returns toward normal. The atrophy of the cortex in the tests might be explained by supposing the suprarenals to be intimately concerned in the utilization of fats, that with fat absent from the diet a large portion of their functional duties is removed, thereby resulting in the observed atrophy. But on the basis of this hypothesis it is difficult, if not impossible, to explain why, when fat is again added to the diet, the cortex, resuming its supposed activities, does not increase in weight. Many of the substances used to produce a cure were individual fatty acids or fatty acid esters. In the ordinary diet these compounds are present in various complex mixtures such as butter, lard and others. It may be that the suprarenals separate out essential fatty acids from the mixtures present in the usual diet and that when cure is produced by feeding individual fatty acids this function is perforce inactive. Some of the cured animals, however, were fed butter, corn oil, poppy seed oil and other mixtures, yet their suprarenal weights in general were similar to those of animals cured with methyl linoleate, methyl oleate, linseed oil, methyl arachidonate and other substances. As in the vitamin E deficiency study the only definite conclusion to be drawn from the observations made is that the suprarenals are probably linked in some way with fat metabolism.

While these studies, at the present stage, have failed to elucidate the nature of the relationship between suprarenals and constituents of the diet, they have confirmed certain previous observations and added a new alliance; namely, a relationship to vitamin E and to fat metabolism. McCarrison (1921) writes: "Indeed, it may be said that adrenal derangement is one of the most important of all the effects of food deficiency on the animal organism." Certain it is that when, if ever, the final explanations have been achieved concerning the changes produced in the suprarenals by dietary deficiencies, great strides will have been taken toward the determination of the functions of the suprarenal and other endocrine glands.

SUMMARY

The suprarenals from 176 rats were studied to determine the effects of certain dietary modifications on the estimated weights of the cortex and the medulla of the suprarenal glands. Weights were estimated from serial sections by the paper outline method, and it was shown that sections taken at 240 micron intervals gave average results not significantly different from those with sections at 10 or 15 micron intervals.

1. The first pregnancy in normal Wistar albino rats did not alter the weight of the cortex or the medulla.

2. Rats deprived of vitamin E and killed during the second pregnancy had suprarenals, the cortex of which was questionably hypertrophied, but the medulla of which was definitely atrophied. Rats maintained on a vitamin E deficient diet and carried through a first pregnancy, then refed vitamin E and killed during a second pregnancy, had significantly enlarged suprarenals, due entirely to cortical hypertrophy. The medulla returned to a normal weight.

3. A fat-free diet produced in male and female albino rats a relative atrophy of the suprarenals, due to both cortical and medullary decrease. Curing the symptoms of this diet by feeding fatty acids, chiefly linoleic, did not cause a return of the suprarenal weight to normal. The weight of the medulla did increase, but the cortical weight remained practically unchanged. The differences between cortex and medulla of the various female groups were statistically significant; none of those in the male groups, except the subnormal weight of the medulla in the test group, was significant. The similarity of trend of changes in the male groups as compared with the female groups was the basis for combining male and female results in the summary.

I wish to express my thanks to Dr. C. M. Jackson for his criticism and guidance during the course of this work.

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THE CONSTITUENTS IN NORMAL URINE PRODUCING THE HYPERGLYCEMIA PREVIOUSLY ATTRIBUTED TO PROLAN*

BURT LINCOLN DAVIS, JR., J. C. HINSEY AND J. E. MARKEE
From the Department of Anatomy, Stanford University
STANFORD UNIVERSITY, CALIF.

Böhm (1) reported that the intravenous injection of 100 units of prolan in rabbits caused a hyperglycemia which appeared in 20 minutes and lasted for 90 minutes. These findings were confirmed by Eidelsberg (2). If these observations were valid, this phenomenon could be utilized as a test for pregnancy. After our investigation was under way, Dingemanse and Kober (3) reported that, while the intravenous injection of their crude preparation of prolan caused a hyperglycemia, massive doses (as much as 1000 units per kg.) of a highly purified prolan caused a slight hypoglycemia.

These studies have been concerned with a search for the hyperglycemic agents contained in normal urine which in our estimation explain the results reported by other investigators when crude prolan was injected. Normal adult male and female rabbits (2.5 to 5 kg.) were used. Initial blood samples were taken from the marginal ear vein, the various substances with possible hyperglycemic action were injected, and then analyses were made on samples of blood taken at intervals of 10, 20, 30, 40, 50, 60 and 90 minutes post-injection. The reducing sugar content of the samples was determined by the method of Folin (4). As our work progressed, various other experiments were performed in an endeavor to determine the mode of action of some of the hyperglycemic agents. These will be described later in their proper place. Although many of our negative results could be construed as controls, we have run in addition controls in which the injections consisted of normal saline.

Reference to Table 1 shows that normal male urine as well as pregnancy urine and a crude extract of prolan (prepared by the method described by Engle [5]) all have a hyperglycemic effect. It is interesting to note that this hyperglycemic agent in crude prolan could be destroyed by boiling. The fact that it was present in the urine of a two-year-old male child as well as in urine from adult males would indicate that it was not prolan. That the hyperglycemia is not due to ovarian changes is shown by the occurrence of a similar rise in blood sugar following the injection of male urine into recently ovariectomized females (less than three weeks following ovariectomy).

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TABLE 1*

PROLAN, MALE, AND FEMALE URINE

Experiments		0 Min.	10 Min.	20 Min.	30 Min.	40 Min.	50 Min.	60 Min.	90 Min.
8	Crude prolan, 50 units	100	120	128	124	116	116	115	109
2	Crude prolan, 2 units	100	116	113	110	109	108	106	105
4	Crude prolan, boiled 30 minutes	100	102	104	99	100	100	99	101
3	Crude prolan, 50 units into ovariectomized rabbits	100	113	137	144	140	133	127	110
14	Pregnancy urine (2½ cc. per kg.)	100	113	119	117	114	107	107	100
13	Male urine into males and females (2½ cc. per kg.)	100	118	119	116	107	102	102	99
4	Urine from a 2-year-old male child (2½ cc. per kg.)	100	111	121	120	114	112	111	108
8	Male urine into ovariectomized rabbits (2½ cc. per kg.)	100	114	114	110	107	103	103	106

*The blood sugar changes are represented in these tables in percentages, taking the initial reading as 100%. The percentages in these tables represent averages of the readings from the number of experiments indicated in the first column.

TABLE 2

ANTUITRIN S

Experiments		0 Min.	10 Min.	20 Min.	30 Min.	40 Min.	50 Min.	60 Min.	90 Min.
3	100 units into adult females	100	102	101	103	100	100	99	99
2	50 units into adult females	100	97	102	101	102	102	100	100
6	100 units into 7 weeks rabbits	100	105	104	102	102	103	104	103

The data in Table 2 show that the injection of a highly purified commercial preparation of prolan (antuitrin S) does not cause a hyperglycemia. The observations recorded in these first two tables show that the hyperglycemic agent is probably a normal constituent of urine. That such is the case is shown in Table 3, where it may be seen that uric acid, hippuric

TABLE 3

URIC ACID, HIPPURIC ACID, AND THEIR SODIUM SALTS

Experiments		0 Min.	10 Min.	20 Min.	30 Min.	40 Min.	50 Min.	60 Min.	90 Min.
10	Uric acid (1.5 mg. per kg.)	100	123	116	113	106	106	102	102
6	Na urate into recently ovariectomized rabbits (4.5 to 5 mg. per kg.)	100	117	121	118	116	113	107	108
4	Boiled sodium urate	100	101	104	104	104	108	105	105
15	Hippuric acid (1.5 to 3.0 mg. per kg.)	100	114	112	109	106	104	104	103
4	Na hippurate (3.5 mg. per kg.)	100	107	108	110	106	100	104	100
5	Na hippurate into long interval ovariectomized rabbits	100	98	99	102	103	101	101	98

acid and their sodium salts all produce significant rises in normal males and females and in recently ovariectomized rabbits (up to 3 weeks). However, sodium hippurate does not cause a rise in the blood sugar level in rabbits that have been ovariectomized for over two months. It should also be noted that boiled sodium urate failed to induce a hyperglycemia as did the boiled crude prolan.

In order to demonstrate the mode of action of these substances, male urine, sodium urate and sodium hippurate were administered to animals whose adrenal medulla had been destroyed by cauterization (Table 4).

TABLE 4

ADRENODEMEDULLATED AND PARTIAL CHORDECTOMY (T4 through L2)

Experiments		0 Min.	10 Min.	20 Min.	30 Min.	40 Min.	50 Min.	60 Min.	90 Min.
9	Male urine (adrenodemedullated)	100	96	96	94	95	94	97	99
3	Na urate (4.5 to 5.0 mg. per kg.) (adrenodemedullated)	100	105	101	100	100	101	106	103
3	Na hippurate (3.5 mg. per kg.) (adrenodemedullated)	100	102	99	104	97	100	105	102
4	Male urine (chordectomized)	100	106	122	122	114	113	104	109

These experiments gave negative results throughout; in fact, there was a slight tendency for the male urine to cause a decrease whereas sodium urate and hippurate elicited no such response. This slight hyperglycemia may be attributed to the known effects of certain other constituents of urine (Underhill [6, 7, 8], Elias, et al. [9], Hill and Mattison [10]). In order to remove the thoracolumbar sympathetic innervation of the adrenal medulla, the spinal cord was removed from the 4T through the 2L segments in a group of animals (method described by Hinsey and Markee [11]). In contrast to the negative findings in the animals deprived of the adrenal medulla, in all four experiments where the secretory innervation of the adrenal medulla was excised, there was a typical hyperglycemic response. This shows that the activation takes place in the absence of the thoracolumbar sympathetic innervation of the adrenal medulla and that the site of action is probably peripheral to the central nervous system.

One of the most baffling phenomena observed in the work was that no hyperglycemia was produced when male urine, pregnancy urine or uric acid was injected ten days after massive doses of antuitrin S or crude prolan (Table 5). A similar phenomenon occurred when male urine was

TABLE 5

THEELIN, AND INHIBITION CAUSED BY PROLAN, ANTUITRIN S, AND THEELIN

Experiments		0 Min.	10 Min.	20 Min.	30 Min.	40 Min.	50 Min.	60 Min.	90 Min.
5	Male urine 10 days after 50–100 units Antuitrin S (per kg.)	100	98	99	96	96	95	94	90
6	Pregnancy urine 10 days after 50 units crude prolan (per kg.)	100	101	102	102	102	101	99	100
2	Uric acid 10 days after 50 units crude prolan (per kg.)	100	91	94	97	98	100	104	101
5	100 units of theelin intravenously (per kg.)	100	91	92	97	99	99	98	98
4	Male urine after 500 units of theelin in 48 hours	100	99	105	105	109	112	106	109

injected into normal females that had received 500 units of theelin in the preceding 48 hours. The injection of 50 to 100 units of theelin produces a slight transient hypoglycemia when injected into normal females.

Table 6 includes the data obtained from experiments in which physiological saline as well as urea and creatinine (in approximate concentrations in which they are found in urine) were injected.

TABLE 6

SALINE CONTROLS AND OTHER SUBSTANCES IN URINE

Experiments		0 Min.	10 Min.	20 Min.	30 Min.	40 Min.	50 Min.	60 Min.	90 Min.
4	Normal saline (2½ cc. per kg.).....	100	99	99	97	97	96	100	99
2	Urea (62.5 mg. per kg.).....	100	100	99	100	97	97	92	94
2	Creatinine (2.5 mg. per kg.).....	100	100	103	102	100	103	102	105

SUMMARY

1. Hyperglycemia was induced in rabbits by the injection of a crude preparation of prolan (13 experiments) and untreated pregnancy urine (14 experiments).

2. It was also induced by the intravenous injection of urine from mature human males (21 experiments) and a two-year-old male infant (4 experiments). It was also obtained when male urine was injected into ovariectomized rabbits up till three weeks after the operation (8 experiments), but was absent when sodium hippurate was injected two months after ovariectomy (5 experiments).

3. It was not induced by the intravenous injection of 50 to 100 rat units of a highly purified commercial preparation of prolan, antuitrin S (11 experiments).

4. It was induced by the intravenous injection of uric acid (10 experiments), sodium urate (6 experiments), hippuric acid (14 experiments), and sodium hippurate (4 experiments).

5. It was not induced by the intravenous injection of two units of crude prolan (4 experiments) or sodium urate (4 experiments) when these substances had been boiled for 30 minutes.

6. It was not induced in rabbits in which the medulla of the adrenal had been destroyed by electric cautery either by the injection of male urine (9 experiments), nor sodium urate (3 experiments), nor sodium hippurate (3 experiments).

7. It was induced by the intravenous injection of male urine into rabbits in which the spinal cord had been removed from 4T down through the 2L level, inclusive (4 experiments).

8. The intravenous injection of theelin (100 rat units) produced a slight transient hypoglycemia (5 experiments).

9. During pseudopregnancy (10 days after the injection of 50 to 100 units of antuitrin S per kg., and in some 50 units of crude prolan per kg.), male urine, pregnancy urine and uric acid failed to produce the hyperglycemia (13 experiments).

10. Intravenous injection of male urine into animals that had received 500 units of theelin subcutaneously in the previous 48 hours also failed to induce a hyperglycemia (4 experiments).

11. Hyperglycemia was not produced by the injection of normal saline (2.5 cc. per kg. in 4 experiments), urea (62.5 mg. per kg. in 2 experiments) and creatinine (2.5 mg. per kg. in 2 experiments).

CONCLUSIONS

1. The hyperglycemia produced by urine injection into rabbits is due to urinary constituents other than prolan, i.e., uric and hippuric acids and possibly other substances.

2. It cannot be elicited in pseudopregnant rabbits or in rabbits which have received massive doses of follicular hormone.

3. It depends upon the presence of the adrenal medulla even though it does occur when the adrenal medulla has been deprived of its thoracolumbar sympathetic innervation.

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ENDOCRINE DWARFISM

SECOND REPORT

WILLIAM ENGELBACH, M.D.,* AND ROBERT L. SCHAEFER, M.D.
DETROIT, MICHIGAN

In our preliminary report (1), the clinical classification and diagnostic signs for endocrine dwarfism were given, and the preliminary response to treatment of a selected group of patients was reported.

The seven cases detailed in the first table showed what we deemed a favorable response at the time. Their duration of treatment was from three to five months, and the increase in statural height varied from 1.0 to 2.7 inches during this period.

To dispel any doubt as to the specificity of the medicament, Antuitrin-G†, all patients were placed under a control period from two to six months, during which time no increase in height was noted except in Case 5, and this was but 0.5 of an inch over a five-month interval. Their clinical histories over a protracted period of time suggested a stationary growth or a very minimal growth, nothing as compared with the results in our first or second charts. Their histories also denote the fact that *they had been treated with thyroid extract and other glandular products by mouth without showing any such growth stimulation.* It should be remembered that they are truly dwarfs, their measurements being far below the minimal normal, and that their response to therapy was markedly in excess of their normal growth increment. No such previous results have ever been recorded with any form of therapy, including thyroid extract alone or combined with any pluriglandular type of treatment in this type of dwarfism.

Since the publication of the first report, Patients 1, 2, and 6 have discontinued treatment. Patients 1 and 2 discontinued because no further satisfactory growth increment was noted after several months more of treatment. In their instances we concurred with their physicians for the following reasons. Patient 1, diagnosed hypopituitarism, aged thirteen and one-half years, showed normal roentgenographic studies for osseous development. Sex development and function was also normal for his age. Patient 2, diagnosed hypothyropituitarism, aged fifteen years, showed roentgenographic studies for osseous devolepment in advance of that of the normal. Her sex development and function were approaching maturity as demonstrated by normal rhythmic periods for three years. The administration of the growth hormone resulted in the production of an amenorrhea on two occasions.

*This work was initiated previous to Dr. Engelbach's death.

†Antuitrin-G is a product not yet commercially available and was supplied to us by the Research Laboratory of Parke, Davis and Company for a preliminary research test. The letter "G" is used to differentiate the growth from the sex factor.

TABLE I

Endocrine Growth Development
Favorable Response

Case No.	Sex	Before Treatment: Age		Actual Height	Normal Variations		Length of Control Period	Change in Height During Control Period	Osseous Development	Type of Deficiency	After Treatment: Duration of Treatment	Height	Gain in Height	Remarks
		Year	Month	Inches	Min. Inches	Max. Inches	Month				Month	Inches	Inches	
1	M	13	6	55.0	57.8	61.8	4	None	Normal	−P	3	56.5	1.5	B. M. R., 0%
2	F	15		58.7	60.4	64.6	2	None	Slight advance	−TP	3½	59.7	1.0	B. M. R., −12%
3	M	11		47.5	53.3	57.1	3	None	Delay 4 years	−TP	4½	50.2	2.7	No B. M. R. Marked subjective improvement. Chondro-epiphysitis.
4	F	9	5	42.7	50.1	53.7	2	None	Delay 3 years	−TP	3½	44.2	1.5	Marked subjective improvement. Chondro-epiphysitis. Enlarged thymus.
5	M	18	6	52.5	64.9	69.3	5	Gain of .5 inch.	Delay 3 years	−PT	5	55.7	2.7	B. M. R., −20%
6	M	14	7	52.0	59.5	63.7	2	None	Delay 2 years	−PT	3½	54.7	2.7	B. M. R., −10%. Mentality improved.
7	F	7	4	36.7	45.2	48.4	6	None	Delay 1 year	−P	3	38.5	1.8	B. M. R., −7%

−P denotes hypopituitarism.
−TP denotes hypothyropituitarism.
−PT denotes hypopituitarothyroidism.

This coincides with our views presented at the time of the preliminary report, namely, that in the presence of normal sex development and function, or of normal or advanced osseous-development, therapy with this hormonic substance would probably be of little or no value. We believe that there is an antagonism between the sex and growth factors elaborated by the anterior lobe of the pituitary gland. Evidence of this was noted by treating a male dwarf at the age of thirty-four years. His libido and potentia, which were normal before treatment, were entirely abolished. Supporting evidence, too, can be deduced from the normal growth increment curve, which tends to prove that at the time of adolescence over ninety per cent of human growth has been attained. This is no doubt due to some influence of the gonads upon the various epiphyses resulting in their closure with consequent cessation of growth. Any stimulative effect produced by growth hormone after sex maturity would result, no doubt, in a picture similar to that of postadolescent acromegaly because only such osseous structures as the flat bones whose growth originates from the periosteum could be stimulated.

Patient 6, diagnosed hypopituitarothyroidism, aged fourteen years and seven months, had what was considered a favorable therapeutic response. He showed an increase of 2.7 inches in statural height. Because of the fact that his roentgenographic studies for osseous development showed a delay of two years, and his sex development and function were not completed, further treatment was advised. However, cooperation could not be obtained and treatment was discontinued.

The four patients whose cases were outlined in the second table have been under treatment continuously, receiving both antuitrin-G and thyroid extract, except Patient 7. She exhibited no signs of hypothyroidism and received antuitrin-G alone. The duration of treatment varied from four-

TABLE II

ENDOCRINE GROWTH DEVELOPMENT

Case No.	Age		Sex	Actual Height Before Treatment Ins.	Duration of Treatment Mo.	Present Height Ins.	Gain in Height Ins.	Osseous Development	Remarks
	Yr.	Mo.							
3	12	6	M	47.5	15½	52.2	4.7	Advance	Improvement of chondro-epiphysitis. Improved generally. More alert attitude. Increased activity. Improvement in gait.
4	10	9	F	42.7	14	46.0	3.3	Advance	Marked general mental and physical improvement.
5	20	4	M	52.5	15½	59.0	6.0	Not reported	Improved generally. Increased appetite and activity.
7	9		F	36.7	14	40.5	3.8	Slight advance	Improved generally. More alert. More active. Increased appetite. Excellent health past year.

teen to fifteen and one-half months. Their increase in statural height was from 3.3 to 6.0 inches.

Bearing in mind the fact that during the control period of observation without treatment there was no such increase noted (with the one exception cited, Case 5) and comparing this with our end results, the assumption is not unwarranted that their response has been favorable and specific. Too, if these patients continue under observation, it seems probable that they can be made to attain, eventually, an approximately normal growth until epiphyseal closure is effected.

It is a significant fact that in all four of these cases and also in Case 6 of our preliminary report there was a definite retardation in osseous development. This delay varied from one to four years. The subjective findings, while not so reliable in clinical experimentation, are, nevertheless, important to both the physician and the patient. There was, in general, an increase in appetite and physical vigor, presumably a result of somatic stimulation by this growth-promoting substance. An opposite type of history is obtained, usually, in the dwarf type of child. Growth does not take place properly and hence the patient does not require an increased food intake such as is necessary for a normally growing child.

The unusual and significant roentgenographic finding which we first noted in our preliminary report has been only partially described. It has been present in nine of fifteen cases so far observed.* This condition has been previously termed generalized chondro-epiphysitis by the radiologists. It is characterized by fuzzy, ragged, poorly outlined appearance of the osseous centers and epiphyses together with decreased bone density. The follow-up skiagrams, as demonstrated by the above figure, now show that the shafts, also, were involved. Their appearance is characterized principally by a lack of normal bone detail. Comparison of these two roentgenograms, A, before treatment, and B, fifteen and one-half months after treatment, shows an acceleration in the growth and time of appearance of the various centers. This can be noted in the proximal epiphysis of the fibula, which was at first barely discernible, and after treatment it is almost normal in size and development for the age. The other centers after treatment are much more regular in outline and more dense. Their fuzzy, hazy appearance is now assuming that of the normal. The marked change in the shaft now can also be noted. There is normal differentiation between the cortex and medulla, which was lacking in the picture of the untreated patient. The film of this patient after treatment presents comparatively normal bone trabeculation and detail. It is suggested that this roentgenographic finding may prove of both diagnostic and prognostic value during the course of treatment.

The dosage of antuitrin-G has remained the same as previously reported, 2 cc. being given two or three times each week intramuscularly.

*Three additional cases were seen through the kind permission of Dr. Margaret Frazer at the Out-Patient Department of Grace Hospital, Detroit.

We believe that this is adequate and should result in a favorable therapeutic response if the case has been properly selected, admitting that further purification may give even better results. We also maintain that thyroid therapy to tolerance is a valuable adjunct and should always be given in an optimal dosage. Three of the foregoing cases studied displayed definite clinical findings of hypothyroidism. Therefore, we empirically gave thyroid extract not only *during the control period* but throughout. Previous animal experimentation tended to show a marked inter-relationship between the

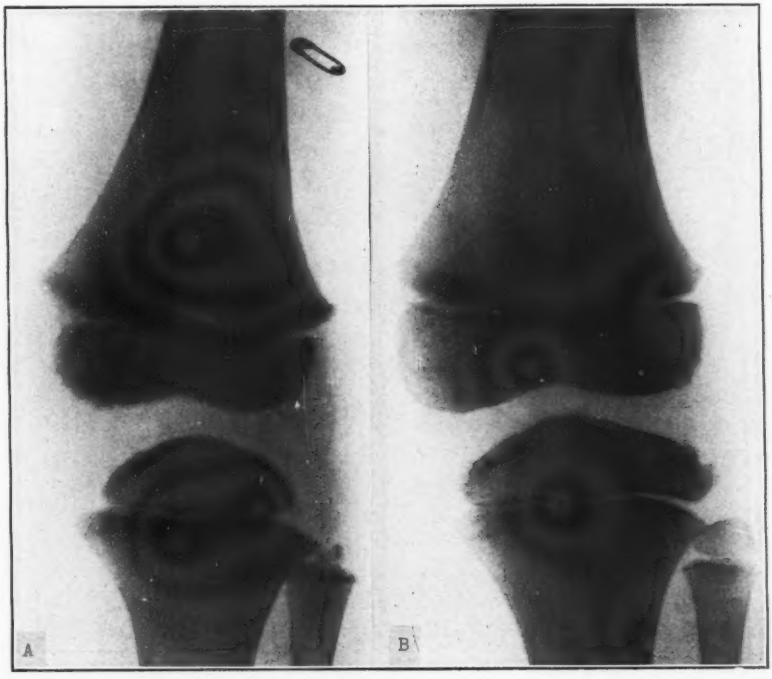

Figure 1. Comparative skiagrams of the knee of Patient 3. A, before treatment. B, fifteen and one-half months after treatment.

thyroid and the pituitary, and, therefore, we believed that this biglandular form of treatment should enhance our results. The recent striking animal experimentation by Smith (2) is pertinent and informative. He has demonstrated in the hypophysectomized immature rat that thyroid extract and growth hormone together result in greater growth stimulation than when the growth hormone alone is given.

A few additional subjects have been treated during the interim but not for a sufficient period to report at this time.

In a case of pituitary cachexia treatment was also given. The myasthenia of the patient was so pronounced at the time he was first seen that the simplest muscular activity, such as shaving, would bring on complete

exhaustion. Suprarenal cortex extract was administered for one month without benefit. Following this treatment he was given the growth hormone for three months which enabled him to carry out ordinary physical tasks and partially resume his occupation.

SUMMARY

Four cases of dwarfism are cited in which the subjects were made to grow in stature at a rate in excess of that normal for their ages. Subjects 3, 5, and 7, showing definite clinical signs of hypothyroidism, received thyroid extract to tolerance in addition to the growth hormone. Subject 7, exhibiting no signs of hypothyroidism except retardation in osseous development, received the growth hormone alone. In Cases 1 and 2 treatment was discontinued because of the poor response which we deemed due to beginning epiphyseal closure together with normal sex development and function. In Case 6 cooperation could not be obtained despite the satisfactory response to treatment, and it was also discontinued. In nine of fifteen cases observed there were the chondro-epiphyseal changes described.

CONCLUSIONS

1. Endocrine dwarfism, if diagnosed sufficiently early, is amenable to specific therapy.

2. Results are enhanced by the combined administration of thyroid extract and the growth hormone.

3. A significant diagnostic and prognostic roentgenologic finding is noted.

4. Retardation in osseous development is apparently a favorable roentgenologic finding.

5. Sex development and sex maturity are unfavorable signs.

NOTE: We are greatly indebted to the following physicians. Without their aid this study would have been impossible. They not only administered the medication but were most cooperative in reporting their observations. Dr. John H. Rowland, New Brunswick, New Jersey. Dr. George E. Brockway, Brooklyn, New York. Dr. Robert Sosler, Brooklyn, New York. Dr. Wm. F. Leigh, Pottsville, Pennsylvania. Dr. B. S. Oppenheimer, New York. Dr. Roger H. Dennett, New York. Dr. Leo G. Christian, Lansing, Michigan.

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THE ACTION OF THE ADRENAL CORTICAL HORMONE ON THE ELIMINATION OF CHOLESTEROL BY THE BILE

G. MARAÑON, J. COLLAZO, L. GAETAN AND E. RODA
From the Institute of Medical Pathology of the General Hospital of Madrid
Director: Prof. G. Marañon
and
Central Laboratory of the General Hospital of Madrid
Director: Dr. J. Mouriz

In a previous article (1) we reported studies on the blood cholesterol in diseases of the suprarenal glands. It was shown that hypocholesterinemia coincides with insufficiency of said glands, whereas with a hyperfunction of these organs there is almost always an evident hyper-cholesterinemia. We have also studied (2) the action of the cortical hormone—prepared according to the method of Swingle and Pfiffner ("Corthormona" Ibys)—and shown that after injecting this preparation, which is absolutely free from adrenaline, the blood cholesterol increases considerably in the majority of cases. The increase lasts for 30 to 60 minutes after the injection, but the cholesterinemia varies with the conditions of preparation and age of the product and also with the normal or abnormal state of the organism in which it is injected.

As hematic cholesterol is mainly eliminated by the bile, we have considered it interesting to study the influence exercised on this elimination by the corthormona. Our preliminary findings have been given in papers published earlier this year (3, 4). We now propose to summarize and complete our previous data.

According to Thannhauser (5), the amount of cholesterol eliminated by the bile in cases of biliary fistula is from 0.003 to 0.097 per cent. Cholesterol in the bile obtained by duodenal catheter amounts to 0.2 or 0.6 per cent. These amounts increase when the blood cholesterol increases, and this is comprehensible because the biliary ducts, as eliminatory organs, are the principal regulators of the cholesterol level. It is for this reason also, when the biliary passages become clogged, the level increases considerably. Likewise, cathartics which increase biliary secretion lower the blood cholesterol (6, 7).

There has been very little research on the action of hormones in the biliary elimination of the cholesterol. It mostly refers to thyroid secretion, which has an evident action on the blood cholesterol, according to several authors. Levy and Levy (8) believe this action would clearly tend to reduce the hematic cholesterol, and for this reason they suggest a thyroid treatment for such hyper-cholesterinemic diseases as arterio-sclerosis. They have been able to reduce the blood cholesterol to normal proportions in arterio-sclerotic patients suffering from hyper-cholesterinemia. In a future

paper we propose to discuss these results. According to Parhon and Gherta Werner (9), thyroid secretion would increase the biliary elimination of cholesterol. Leites and Ysabolinskaja (10) have also observed that the thyroid hormone increases the concentration of biliary cholesterol, and this process lasts for 20 to 24 hours. Other hormones (insulin, parathyroid and pituitary) do not possess this action. The authors, therefore, suggest that the reaction is characteristic only of the thyroid hormone and they raise the question whether an excess secretion of the thyroid may intervene in the genesis of chololithiasis.

With reference to the influence of the cortical hormone on biliary cholesterol, we find no data beyond that of Rothschild, mentioned by Landau (11), to the effect that he could observe an increase in the cholesterol in the bile of animals deprived of their suprarenal glands.

Our experiments with "Corthormona" were carried out on adult patients from whom bile was extracted by duodenal catheter. The average amount obtained during fasting was from 0.08. The amount of bile extracted before breakfast was noted. On the following day the bile was again extracted two hours after an intravenous injection of 5 cc. of "Corthormona." At the same time the cholesterinemia was ascertained. The results are shown in Table I.

TABLE I

ACTION OF "CORTHORMONA" (5 CC. INTRAVENOUS) ON BILIARY AND HEMATIC CHOLESTEROL.

Numbers	Diagnosis	Previous mgm./100 cc.	60′ After Injection mgm./100 cc.	120′ After Injection mgm./100 cc.	Maximum Change from Initial Figure mgm.
I–46–49	Espondilitis.....	Blood 220 Bile 130	150	210 200	− 70 + 70
II–48–6	Maltese fever.....	Blood 190 Bile 65	180	170 118	− 20 + 53
III–46–7	Slight Addison.....	Blood 100 Bile 44	200	160 94	+100 + 50
IV–47–1	Tuberculosis..... (Pulmonary)	Blood 130 Bile 50	110	120 47	− 20 − 3
V–47–2	Tuberculosis..... (Pulmonary)	Blood 130 Bile 88	120	140 120	+ 10 + 32
VI–46–1	Tuberculosis..... (Pulmonary)	Blood 150 Bile 130	120	130 400	− 30 +270
Averages...	.....	Blood 153 Bile 84	146	155 163	− 7 + 79

This table shows us, in the first place, that the hyper-cholesterinemia produced by the "Corthormona" in these cases was relatively slight; this occurred with all the "Corthormona" of this batch and again shows how important is the preparation of this product, and how varied the results of its action may be.

The increase of biliary cholesterol is evident. There is no proportion between it and the amount of cholesterol in the blood. The highest figures

in the bile do not correspond to the greatest hyper-cholesterinemias, nor do the lowest eliminations correspond to the smallest hypo-cholesterinemias.

We hasten to call attention to the fact that there may be errors in this research on the duodenal bile. The figures obtained have only an approximate value, as we have to work on any biliary flux which the catheter may collect, but there is absolutely no indication of quantity.

For this reason we have carried out another series of experiments on dogs, operated on for biliary fistula by marsupialization. When the wound was healed and the general condition of the animal was again good, we determined the amounts of cholesterol in the blood and in the bile, during fast, and afterwards at intervals of 15, 30, 45, 60 and 90 minues after an intra-muscular injection of from 8 to 15 cc. of fresh "Corthormona." The following Table II shows the results obtained:

TABLE II

CURVE OF COLESTEROL IN BLOOD AND BILE OF DOGS, UNDER INJECTION OF "CORTHORMONA"

Dog No.	Biological Material	Before Injection mgm./ 100 cc.	15′ After mgm./ 100 cc.	30′ After mgm./ 100 cc.	45′ After mgm./ 100 cc.	60′ After mgm./ 100 cc.	90′ After mgm./ 100 cc.	Notes	Maximum Change mgm.
1	Blood.....	179.	192.	202.	.....	185.	164.	15 cc. intramuscular injection	+23
	Bile.....	20.8	22.6	25.4	.....	27.3	24.3		+ 6.5
2	Blood.....	176.	179.	.....	.....	200.	206.	10 cc. intramuscular injection	+30
	Bile.....	44.1	44.7	.....	.....	60.5	62.2		+18.1
3	Blood.....	164.5	191.6	211.6	185.	175.	.....	8 cc. intravenous injection	+47.1
	Bile.....	22.8	.....	35.7	.....	32.8	22.8		+12.9
4	Blood.....	150.	189.	210.	160.	133.	.....	8 cc. intravenous injection	+60
	Bile.....	19.8	.....	26.6	.....	25.2	24.2		+ 6.8
5	Blood.....	150.	193.	203.	150.	.....	150.	15 cc. intravenous injection	+53
	Bile.....	19.8	23.8	28.	.....	.....	27.2		+ 8.2
Average...	Blood.....	163.9	188.9	206.6	.....	173.	173.		+42.7
	Bile.....	25.4	30.3	32.0	.....	36.4	32.1		+11.0

This table confirms, in the first place, the hypercholesterinemic action of "Corthormona."

In addition, it confirms the increase of the proportion of biliary cholesterol due to the action of "Corthormona," which was already observed in human beings with duodenal catheter extraction. We have been unable to find changes in the total amount of bile eliminated through the fistulas of these dogs subjected to injections; in consequence, the hormone has no cholagogue action.

We also find no parallel here between the cholesterinemia figure and the intensity of elimination of the cholesterol by the bile.

There appears to be no ratio between the development of these two curves. The hyper-cholesterinemia reaches its maximum in about 30 minutes; the cholesterol in the bile attains its highest figure about 60 minutes after the injection. After the normal figure of the cholesterinemia has been reached the increased elimination by the bile still continues. An hour

after the experiments were finished, that is to say, 90 minutes after the injection, the hyper-secretion of cholesterol in the biliary flux still continued. During the tests on human subjects we noted that the hyper-elimination of bile continued two hours after the injection.

SUMMARY

Experiments to determine the influence of the adrenal cortical hormone on the cholesterol content of the blood and bile were made. Six human subjects and five dogs were used. It was found that the blood cholesterol increased as did the concentration in the bile.

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THE OCCURRENCE OF PARATHYROID TISSUE WITHIN THE THYMUS: REPORT OF FOUR CASES

L. A. BREWER, III, A.B., M.D.
From the Department of Pathology, University of Michigan
ANN ARBOR, MICH.

Aberrant parathyroid glands have been observed frequently in the thymic tissue of lower animals, but such observations are rare in man. The recent development of parathyroid surgery makes this "thymic" location of the parathyroids of interest to the surgeon as well as to the pathologist and endocrinologist. Four such cases, found in the routine autopsy material of the University Hospital, Ann Arbor, Michigan, are apparently the first to be reported in this country. The four cases include two showing heterotopia of parathyroid in thoracic thymus and two with parathyroid nodules in cervical thymus.

The parathyroids (1) are formed from small dorsal diverticula of the endothelial cells of the third and fourth pharyngeal pouches. These cells lose their attachment to the primitive pharynx by atrophy of the connecting ducts, and are free to migrate caudally so that the pair from the fourth pouch are located on each side in the tunica propria of the medial surface of the lateral thyroid lobes at the level of the cricoid cartilage. The pair from the third branchial pouch migrate farther caudally to the lower border of the thyroid gland, where they are in association with the inferior thyroid arteries or their main branches.

The primitive thymus arises as ventral and medial prolongations on either side from the third branchial pouch. Additional portions are derived from smaller invaginations of the fourth branchial pouch. Following atrophy of the connecting ducts, these cells migrate caudally to form the thoracic thymus. The anlagen from the third pharyngeal pouch form the main portion of the thymus and descend farther caudally in the thorax than the smaller part derived from the fourth branchial pouch (2).

Accessory parathyroid tissue is found with relative frequency in the thymus of lower animals. In 1908 Pepere (3) observed "masses" of parathyroid tissue in thymuses of rats, rabbits, and hedgehogs, stating that Erdheim previously had made similar observations. Pepere believed that these intrathymic nodules were a constant finding and called them "parathyroides internes" to distinguish them from the "parathyroides externes" found outside the thymus. He states that double or single cords of cells are most often seen in the capsule, less often in the interlobar connective tissue, and occasionally in the thymic parenchyma.

Haberfeld and Schilder (4), in 1909, were able to demonstrate accessory parathyroids in all rabbit thymuses examined. In the same year

Meyer (5) showed parathyroid in sheep thymus, and Harvier (6) demonstrated that in the cat, parathyroid glandules may be found in the thymus in fifty per cent of the cases. Two years later Aimé (7) found parathyroid in the thymus of a Greek turtle. In 1920 Farner and Klinger (8) reported accessory parathyroid glandules to be present "as the rule" in the thymus of the cat, either in the capsule or within the parenchyma. The following year Dustin and Gerard (9) made similar observations in reptiles (the crocodile, python, etc.). More recently Shapiro and Jaffe (10) and Nicolas and Swingle (11) have emphasized the frequency of this finding in the thymus of the cat, and its importance in extirpation experiments.

PARATHYROID IN THORACIC THYMUS

The literature on heterotopia of parathyroid into thoracic thymus in man is confined to the writings of two observers. Erdheim (12, 13), in 1901 and in 1904, reported three illustrative cases. These patients, age three, eight, and thirteen months, respectively, were all cretins, showing complete aplasia of the thyroid gland. By making serial sections of the entire cervical and upper thoracic regions, numerous accessory parathyroids were found. In each of these cases, parathyroid glandules, containing typical "principal" and "oxyphile cells," were found in the upper poles of the thymic lobes. No glandular tissue of the thyroid was present in the usual location. However, small colloid-containing cysts, composed of low cuboidal epithelium, were found in relation to the thoracic parathyroid and thymic tissues. It cannot be said definitely that these "cysts" represent misplaced thyroid tissue, as similar structures are often found within the parathyroids.

More recently (1928), Dupérié (14) in routine examination of the thoracic thymus of infants found four included parathyroids in one hundred cases examined. One was a premature infant at the eighth month the others being three and one-half months, seven months, and nineteen months old, respectively. All showed accessory parathyroid nodules in the capsule of the superior horns of the thoracic thymus. None of these subjects were cretins as were all reported by Erdheim, and they showed no other congenital anomaly. The whole cervical and upper thoracic regions were not blocked by Dupérié; only suspicious nodules seen grossly were examined. Thus the figure of four per cent showing heterotopia probably represents a low estimate of the frequency of this condition.

CASE REPORTS

The *first case* is that of H. C. (A-31-AK), a well developed adult white male, aged 48, who was admitted to the Thoracic Surgery Service of the University Hospital with a history of cough and asthmatic attacks since childhood. Roentgenographic studies suggested bronchiectasis and lung abscess. The patient's condition became progressively poorer and his respiration ceased one day following temporary phrenicectomy, eight days after admission.

Post-mortem examination revealed multiple bilateral pulmonary abscesses with early gangrene. Gross examination of the cervical and upper thoracic regions was essentially negative. The parathyroids were not identified grossly at

the time of autopsy, but the neck organs were saved. The thymus was of usual size and was in the normal position, showing fatty atrophy and only very slight amounts of lymphoid tissue.

Routine microscopic sections, cut at right angles to the longitudinal axis of the thymus, showed a moderately hyperplastic persistent thymus with fatty atrophy. In the center of the thymic fat, almost completely surrounded by islets of thymic remains, was a small triangular nodule measuring approximately one millimeter on a side (Figure 1). This nodule was composed of a loose reticulum of large pale cells with clear pale-staining cytoplasm and prominent vesicular nuclei, parathyroid "principal cells." Approximately one-third of this nodule was made up of large cells with granular eosinophilic cytoplasm and small round or oval, centrally placed, deep staining nuclei. These cells formed cord-like structures and were the typical "oxyphile cells" of the parathyroid gland (Figure 2). One other section through the thymus showed a similar oval nodule, measuring one-half by one millimeter, composed of the same "oxyphile cells" and "principal cells" (Figure 3). The former were more diffusely scattered in the cords through the reticulum than in the previously described nodule. No accessory parathyroids were found in the cervical region. The upper pair of parathyroid

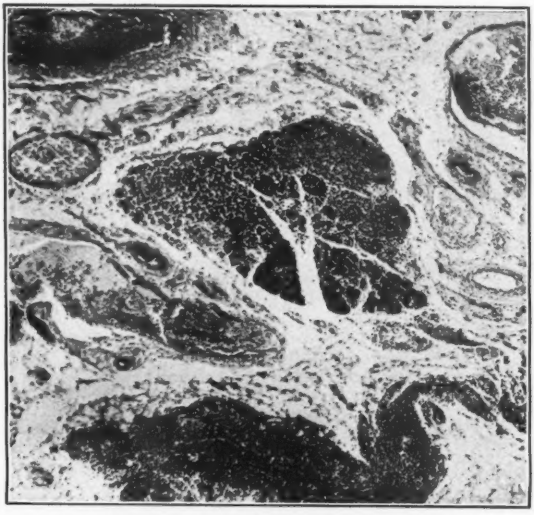

Figure 1. Case 1. Low power view of first nodule of parathyroid in adult thoracic thymus.

bodies were found to be normally placed and showed a histological picture identical with that of the parathyroid glandules in the thymus. The lower pair of parathyroids were missing, so that undoubtedly those found in the thymus represent the lower pair.

The *second case* is that of M. W. (A-46-AK), a 46-year-old white female, who was admitted to the Dermatology Service of the University Hospital, complaining of slightly painful ulcers on the right leg of three years' duration. Similar lesions were found on the neck and right arm. The routine Kahn test was positive (four plus), and tertiary syphilis was diagnosed. The patient died forty-one days after admission.

Post-mortem examination showed syphilitic aortitis, hepatitis, and adrenalitis; syphilitic arteritis of skin, with multiple cutaneous infarctions, secondary infection, and streptococcic septicemia; multiple anomalies (double ureter, accessory pancreas in duodenal wall, and the condition to be described).

Gross examination of the cervical and upper thoracic regions revealed nothing remarkable. The thymus was of the usual size and normally placed. It showed fatty infiltration with small areas of lymphoid tissue.

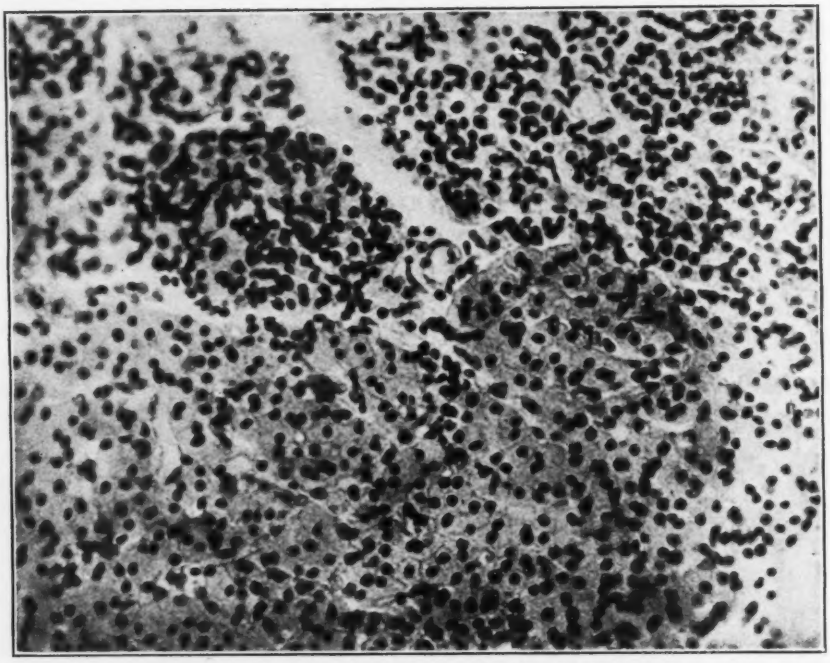

Figure 2. Case 1. High power view of Figure 1, showing "principal" and "oxyphile cells."

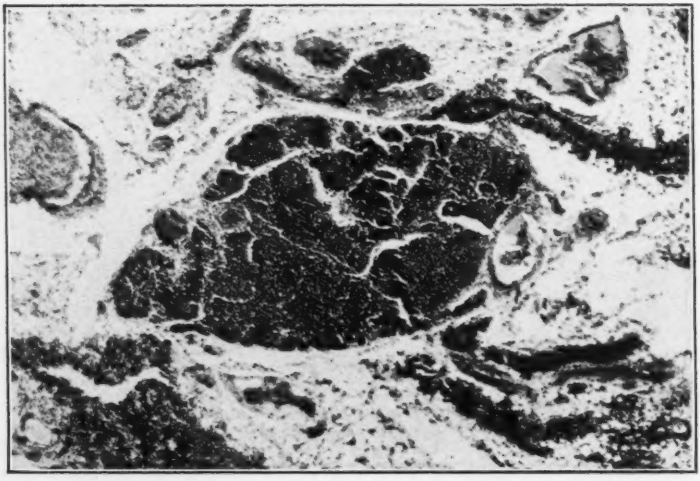

Figure 3. Case 1. Low power view of second nodule of parathyroid in adult thoracic thymus.

Routine microscopic sections were made at right angles to the long axis of the thymus. Extensive thymic remains for the age were noted, with fatty atrophy. In the mid-portion of one section a small, oval islet of tissue, measuring 1.5 by 0.75 mm. was seen (Figure 4). This was composed of large clear cells

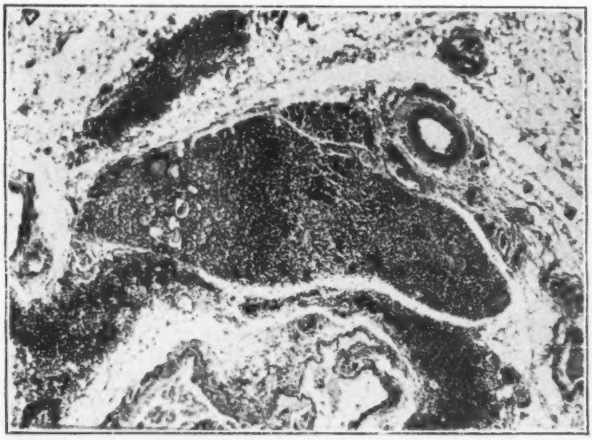

Figure 4. Case 2. Low power view of nodule of parathyroid in adult thoracic thymus, showing small cysts and prominent nests of "oxyphile cells" in a parenchyma of "principal cells."

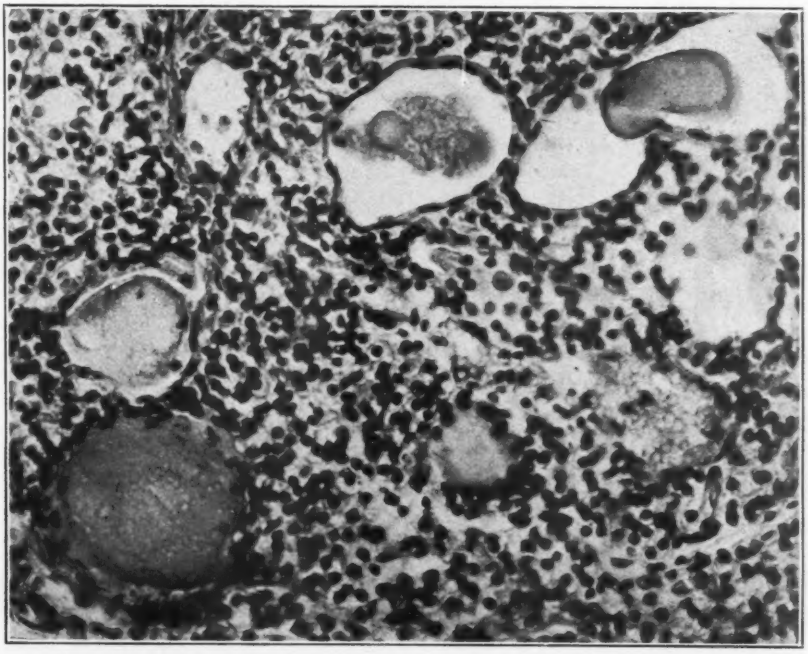

Figure 5. Case 2. Detail view of the cysts in the parathyroid nodule from adult thoracic thymus shown in the preceding figure.

with granular pale cytoplasm and prominent vesicular nuclei. The cytoplasm and cell membranes were so pale that for the most part only the nucleus was seen. These cells were parathyroid "principal cells." A fine fibrous connective tissue reticulum divided this structure into small lobules. Near one end of this nodule of tissue these pale-staining cells formed acini, containing a homogeneous pink-staining substance resembling colloid. Some of the acini were distended by this colloid-like material, so that the epithelium was of the pavement type (Figure 5). There were also several small cords of large cells with deep-staining granular acidophilic cytoplasm and small oval or round, centrally placed, prominent nuclei (Figure 6). These were "oxyphile cells," forming nests similar to those seen in

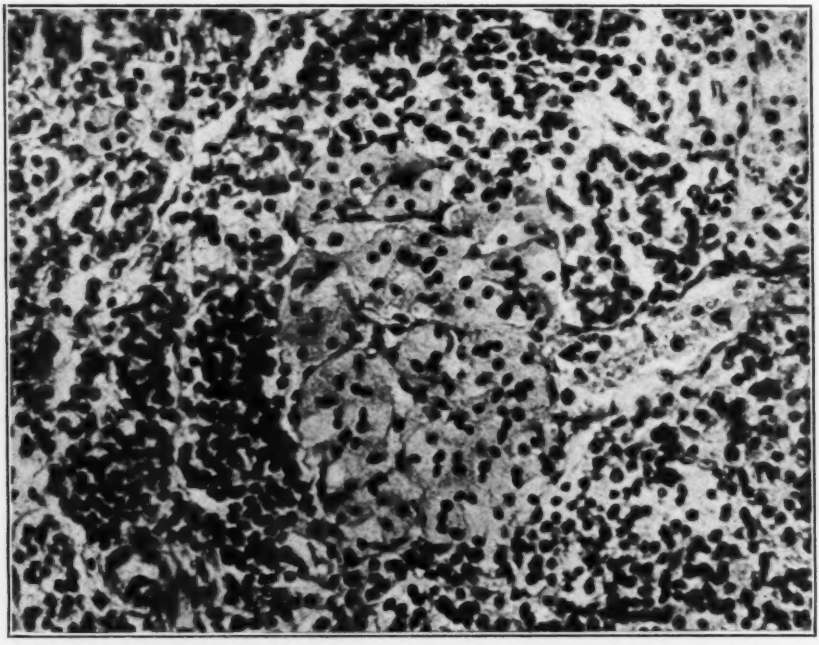

Figure 6. Case 2. High power view showing cords of "oxyphile cells" in the parathyroid nodule shown in Figure 4.

the parathyroid gland. No accessory parathyroid nodules were found in the cervical region. The normally placed parathyroids presented a histological pattern that was an exact counterpart of the parathyroid described in the thymus. One parathyroid of the lower pair was missing, so that the one found in the thymus no doubt represents this gland.

These two cases resemble those previously reported in that they show similar histological relationships between parathyroid and thoracic thymus. They differ markedly in the age groups represented. Those reported by Erdheim and Dupérié were all in infants; two of them premature, and the oldest but nineteen months. Our cases 1 and 2 were adults, aged 46 and 48 years, respectively. The subjects reported by Erdheim showed complete aplasia of the thyroid. Our patients showed no other significant cervical anomalies, although patient 2 showed an anomalous double left ureter and accessory pancreas in the duodenal wall.

The intimate relationship between the parathyroid glandules included in the thoracic thymus of cases 1 and 2 may be explained in that they both represent third branchial pouch derivatives. A small endodermal bud of the parathyroid anlage of the third pharyngeal pouch, which usually forms one of the inferior pair of parathyroids, might well have become attached to the larger thymus anlage of this same pharyngeal pouch. Then "parathyroid metamere III" and "thymus metamere III" could have migrated together caudally, past the fourth branchial pouch derivatives, to lodge in the upper thoracic region.

PARATHYROID IN CERVICAL THYMUS

The literature on parathyroid heterotopia in "undescended" cervical thymus presents but very few cases. Erdheim (13) has reported five examples of this condition. These included a cretin, aged three months, with complete aplasia of the thyroid gland, a 15 cm. fetus, a new-born anencephalus, a new-born, and a three-months-old infant. In each of these cases accessory thymus was found near the upper pole of the thyroid gland. These thymic nodules contained islets of parathyroid, either separated by fine connective tissue septa or contiguous, with tongue-like projections of one tissue extending into the other. Erdheim (13) interpreted these "rests" of thymus and parathyroid as being derived from the fourth branchial cleft. Groschuff (15) had previously reported similar findings in a 4.4 cm. fetus and a new-born child. Forsyth (16), in 1909, presented a microphotograph of a nodule of thyroid, parathyroid, and thymus, all contained in one fibrous capsule, but separated by fine connective tissue trabeculae. There was no description of this case or other comment on this finding, so that it is interesting only as another proven case of this heterotopia in man. To the present knowledge of the author no other cases have been reported since then.

The *third case* to be presented is that of Baby Boy H. (A-15-AJ), who was a full term infant, born in the Maternity Department of the University Hospital. The second day post-partum he had an attack of cyanosis and spastic twitching of the hands, associated with the appearance of small purpuric lesions on the face, neck and left arm. Lumbar puncture yielded bloody fluid. The baby died on the fourth day.

The autopsy revealed extensive hemorrhages in lungs, adrenal medullae, subserous tissues, skin, and meninges, and early acute purulent lobular pneumonia. There was a bifurcation of the fourth right rib at the costochondral junction. The thyroid was of normal size and normally situated. Parathyroids were not seen grossly.

A routine section through the upper pole of the thyroid on the posterolateral surface of the thyroid gland demonstrated a nodule of lymphoid tissue, measuring 2.5 by 1.5 mms., which was surrounded by a connective tissue capsule and contained numerous Hassall's corpuscles (Figure 7). Within this glandule of thymus were two small islands of cells, differing in cell type and in general architecture from the surrounding thymic tissue. One centrally placed islet was composed of a reticulum of large clear cells with almost colorless agranular cytoplasm and relatively large vesicular nuclei (Figure 8). These were the characteristic "principal cells" of the parathyroid gland. No "oxyphile cells" were present. The second insula, peripherally placed in the medial portion of the thymic nodule, was composed of minute acini containing colloid, lined by low cuboidal epithelium. These acini were identical with those of the adjacent thy-

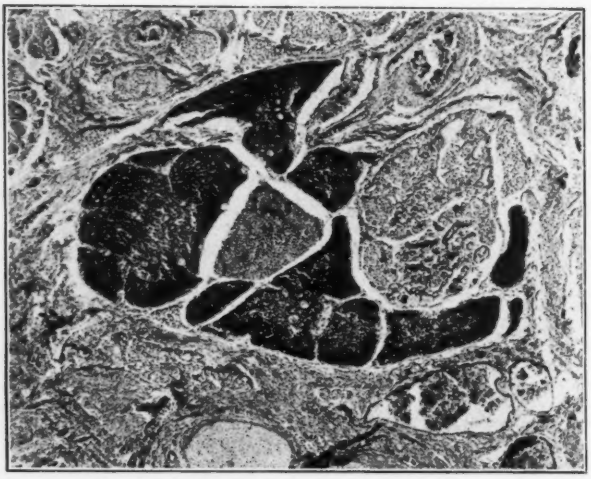

Figure 7. Case 3. Low power view of a cervical thymus (thymus metamere IV) of an infant, containing islets of thyroid and parathyroid.

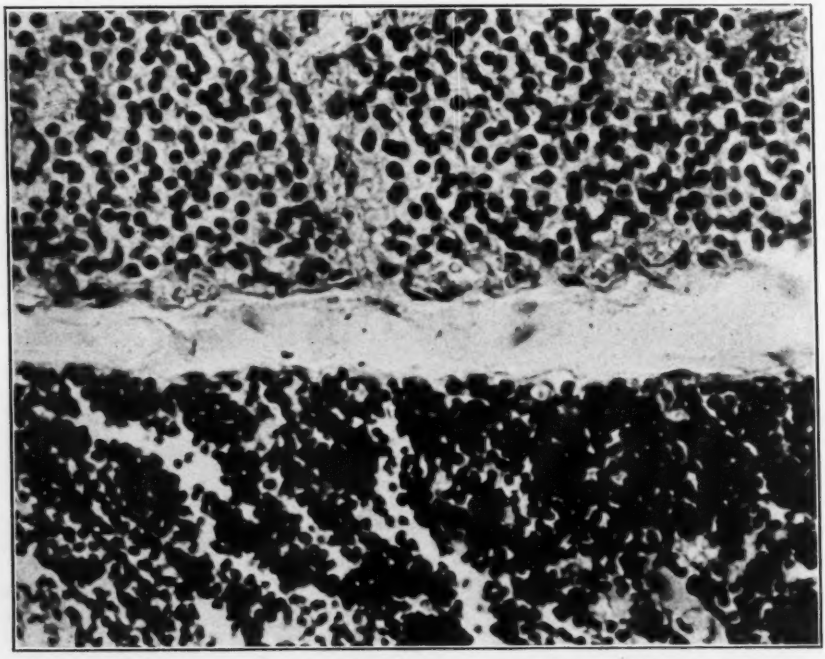

Figure 8. Case 3. High power view of an area from Figure 7. Above are "principal cells" of the parathyroid and below are lymphocytes of the thymus. (The separation of these tissues is an artefact of shrinkage.)

roid gland. Thus this nodule of thymus, with its connective tissue capsule, contained both thyroid and parathyroid.

No similar structure was seen on the opposite side. Small parathyroid nodules at the lower pole of the thyroid showed no such relationship. However, there was one small nodule of cervical thymus, 1.5 mms. in diameter, at the level of the second tracheal ring just posterior to the thyroid gland and lateral to the trachea. The thoracic thymus was in the usual position, extending up as high as about the sixth tracheal ring. It was moderately enlarged. Microscopic examination showed abundant lymphoid tissue, but no other branchial pouch inclusions.

The *fourth case* is that of Baby J. H. (A-18-AK), five and one-half months old, who was admitted to the Fediatrics Service of the University Hospital with a history of cough, failure to gain weight, and an increasing pallor. Three weeks before admission, fever, vomiting and increased coughing developed. The baby died six hours after admission.

At the post-mortem examination the significant findings were bilateral acute purulent bronchopneumonia, with multiple bronchiectatic abscesses in the lower lobe of the left lung, extensive pulmonary atelectasis, and localized emphysema. Gross examination of the cervical and upper thoracic regions showed the thyroid

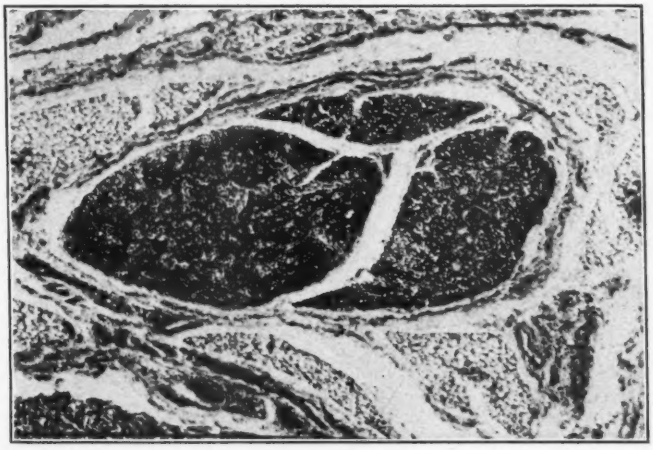

Figure 9. Case 4. Nodule of cervical thymus (thymus metamere IV) from an infant, with included parathyroid.

to be of normal size and in its usual position. No parathyroids were identified. The thymus was in its usual position, being slightly smaller than normal.

A routine section cut through the upper pole of the thyroid showed microscopically a small nodule of parathyroid gland one millimeter in diameter. This nodule was composed of a reticular network of large pale-staining cells with almost colorless cytoplasm and prominent vesicular nuclei. Some of these "principal cells" formed minute acini, which contained small amounts of a colloid-like substance. Similarly placed on the opposite side there was an oval structure, 1.5 by 1 mm., made up of three lobules surrounded by a connective tissue capsule (Figure 9). Two of these small lobules were thymic tissue with well formed Hassall's corpuscles. The third lobule, which extended as a tongue-like projection between the other two, was composed of cells similar to those seen in the opposite parathyroid gland (Figure 10). These cells were somewhat smaller and had more of a tendency to form cords and irregularly shaped nests than on the opposite side. No similar relationships were seen at the lower pole of the thyroid gland. However, one small parathyroid nodule measuring less than one millimeter in diameter was capped with a nodule of thymus tissue, which rested on the parathyroid glandule. These two tissues were separated by the thin fibrous capsule of these glands. Microscopic sections of the thoracic thymus showed no parathyroid inclusion.

Case 3 showed one other congenital anomaly (bifid fourth right rib), while case 4 showed no other anomaly than the described heterotopia. Two of those reported by Erdheim showed marked disturbance in development, aplasia of the thyroid and anencephalus while three others showed no important anomalies. Cases 3 and 4 also fall into the age groups of those recorded by Erdheim. Likewise, cases 3 and 4 are similar to those reported by Erdheim in that cervical thymic tissue was found in intimate relationship to parathyroid tissue at the upper pole of the thyroid gland. He believed that these gland structures were derived from the fourth branchial pouch, since the parathyroid in question in this location was a fourth

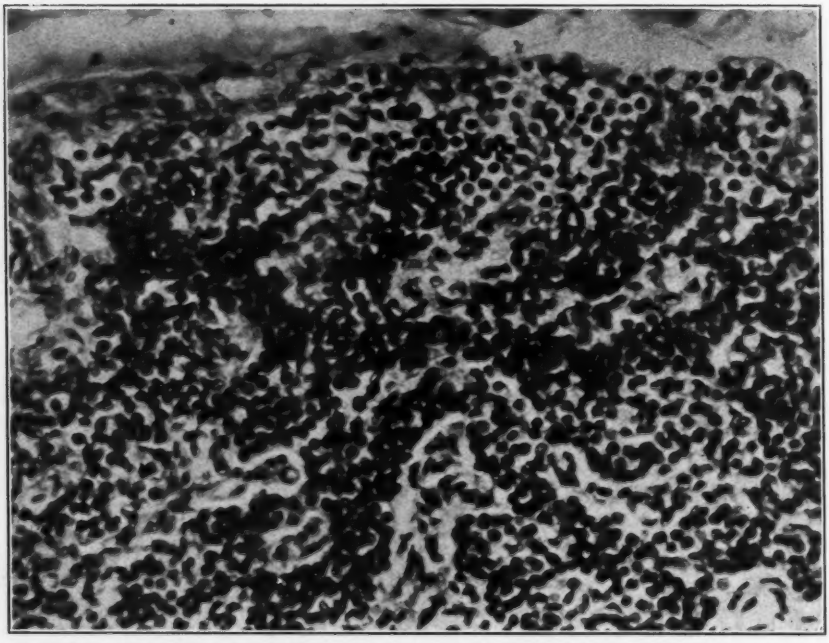

Figure 10. Case 4. High power view of nodule of parathyroid shown in Figure 9, showing cords of "principal cells."

pharyngeal pouch derivative. This belief is further strengthened by the fact that the main and caudal portions of the thymus are derived from the third branchial pouch, as are the inferior pair of parathyroids. The "thymus metamere IV" in these cases, which normally migrates caudally to form the superior part of the thoracic thymus, has then remained in practically the same location, and thus can be found in intimate relationship with "parathyroid metamere IV."

It should be emphasized that the ordinary routine examination of the thymic and cervical regions is incapable of establishing accurate statistics relative to the frequency of parathyroid heterotopia. These heterotopic

islands of parathyroid and thymus are so small as to evade macroscopic detection. If the whole cervical and upper thoracic regions in each of the 400 autopsies performed during the fourteen months in which these cases were observed could have been examined microscopically, the number of cases of heterotopia would no doubt have been greatly augmented.

The inclusion of one or more nodules of parathyroid tissue within the thoracic thymus may be of very great importance. In those cases of osteitis fibrosa cystica and allied conditions in which parathyroidectomy is indicated, the thymic location must be borne in mind upon failure to find the glands in the cervical region. Irradiation or even partial thymectomy might well bring the desired results in selected cases.

SUMMARY

The literature pertaining to heterotopia of parathyroid tissue in the thymus for man and the lower animals is reviewed and four cases showing parathyroid heterotopic in human thymus are presented, with an embryological explanation of the production of the anomalies. The two adult cases presented are probably the first to be reported on this subject. The microscopical structure of the aberrant glands is illustrated. In the two adult cases both "principal" and "oxyphile cells" were present; in the other two no "oxyphile cells" were found. The surgical importance of the inclusion of parathyroids within the thymus is emphasized. The cases reported probably do not represent a true index of the frequency of this condition in this particular series. A more detailed examination of the cervical and upper thoracic regions than can be employed routinely would be necessary in order to demonstrate the actual incidence.

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THE INFLUENCE OF THE PITUITARY ON BASAL METABOLISM AND ON SPECIFIC DYNAMIC ACTION

B. A. HOUSSAY
Institute of Physiology, Faculty of Medicine
BUENOS AIRES

The influence of the pituitary on basal metabolism has been frequently studied in our Institute, papers having been published on the subject in 1930, 1931, 1932 and 1933. In these (1, 9) the bibliographical references on the investigations in different species are to be found.

Most of the experiments in this series have been performed in the dog as has been most of our work on the pituitary, as we wished to make a deeper analysis of the facts in one species. The animals were trained to keep quiet and motionless without anaesthesia or being tied during the tests (1, 2, 10, 11, 17). The air expired during 20 to 30 minutes was analyzed with Haldane's burette. The calories produced were calculated from the oxygen consumed, taking into account the R.Q., and in all cases expressed per square metre per 24 hours. The experimental details are set forth extensively in the papers referred to in the bibliography.

Up to the present the basal metabolic determinations of 27 hypophysectomized dogs have been published, 22 of which were performed in our Institute (several determinations having been made for each dog, 1, 10, 17). In each one of our series the average of basal determination in the hypophysectomized animals was 13 to 16 per cent less than in the controls. The average is —16 per cent for the 27 known cases (see Table 1). The extreme

TABLE 1

BASAL METABOLISM IN NORMAL DOGS

Author	No. of Dogs	Cals./sq. m./day	Author	No. of Dogs	Cals./sq. m./day
Rubner	8	973	Gaebler	1	816
Lusk, Du Bois	11	772	Rapport, Beard	1	784
Kunde	7	777	Plummer, Deuel, Lusk	1	763
Kunde, Steinhaus	7	760	Artundo	5	791
Boothby, Sandiford	4	941	Mazzocco	9	888
Hesse	4	800	Houssay, Artundo	5	804

BASAL METABOLISM IN HYPOPHYSECTOMIZED DOGS

Author	No. of Dogs	Cals./sq. m./day	Author	No. of Dogs	Cals./sq. m./day	Per Cent of the Controls
Benedict, Homans	3	700	Artundo (1930)	8	666	−15.8
Aschner, Porges	1	550	Mazzocco (1932)	9	745	−16.
Gaebler	1	795	Houssay, Artundo (1933)	5	702	−12.6

Average of 27 dogs: 703 cal./sq. m./day. −16 per cent of normal.
In 22 (81%) B. M. was low; in 5 (19%) B. M. was normal or high.

individual values in the hypophysectomized cases were 469 and 931 calories per square metre per 24 hours, but the value was low in 22 (81 per cent) and normal or high in only 5 (19 per cent).

This moderate decrease, very frequent but not constant, of the basal metabolism could be due in hypophysectomized animals either to the alteration in the thyroid function or to the suppression of a pituitary hormone acting directly on the basal metabolic rate.

The thyroid of hypophysectomized dogs shows morphological and functional signs of hypofunction (1, 2, 3). The weight of the gland is decreased, the epithelium low and flattened, almost endothelial; the cells are small, the vesicles of normal width appear dilated, colloid is dense with no central vacuoles and few at the periphery. There are no zones of functional activity as in normal thyroids. After subtotal thyroidectomy compensatory hypertrophy is not produced. Sometimes the walls of the acini break down and large vesicles are so formed. This picture of permanent and intense atrophy is preceded sometimes during the first days by passing signs of postoperative hyperfunction.

Together with these morphological signs there are others of thyroid hypofunction: percentage thyroid iodine raised, a low blood iodine content,* low basal metabolism, an increase in the viscosity and globulin content of the plasma.

In the experiments of Artundo and Mazzocco the hypophysectomized dogs without lowered basal metabolism showed a higher thyroid epithelium (3.4 to 4.2 micromillimetres) than those in which the basal metabolism was decreased (less than 3 micra).

In seven hypophysectomized dogs the metabolism sometimes increased after pancreatectomy, but not constantly (the average determinations were 1164, 774, 723, 590, 1040, 682, 888 calories per sqm. per 24 hrs.). In the controls, with pituitary intact, after pancreatectomy the increase was constant (Houssay and Biasotti, 13).

The diminished metabolism noted in hypophysectomized dogs is not as low as that in athyroidism (Table 2 and Graph 2). Therefore in the hypophysectomized animals there is a decrease but not suppression of the thyroid function (10).

If the thyroid is extirpated in a hypophysectomized animal the metabolism is further diminished; but if the pituitary is extirpated in a thyroidectomized animal this additional diminution does not occur, hence it does not seem that the pituitary has an effect of its own on the metabolism (10). (See Table 2.)

These experiments demonstrate that the pituitary in developing and keeping the anatomic and functional state of the thyroid normal indirectly helps to regulate the basal metabolism. Its metabolic action is continuous (tonic) but exercised by way of the thyroid. This conclusion is corrobo-

*The iodine content of blood markedly increases during the first two or three weeks and then it decreases.

TABLE 2

AVERAGE VALUES OF BASAL METABOLISM IN DOGS. (HOUSSAY AND ARTUNDO, 1933)

	Cals./sq. m./day	Dimin. Per Cent
5 normal	804	.....
7 thyroidectomised	610	−24.1
5 hypophysectomised	702	−12.6
7 hypophysectomised and thyroidectomised	622	−22.2

Four Individual Cases	Cals./sq. m./day	
	①	②
Normal	662	....
Thyrodectomised	565	487
Thyroidectomised and hypophysectomised	603	475
	③	④
Hypophysectomised	609	857
Hypophysectomised and thyroidectomised	472	557

rated by other experiments on the injection of anterior-pituitary lobe extract.

The injection of an alkaline extract of anterior pituitary lobe produces a hyperactivity of the thyroid: the weight of the organ increases, reabsorption of colloid occurs and hypertrophy of the alveolar epithelium, the cells of which enlarge; the iodine content per 100 grams of thyroid diminishes, the blood iodine increases (not in thyroidectomized animals). The basal metabolism rises and the sensitivity to anoxemia is increased, etc.

Table 3 clearly shows the large increase in metabolism produced by the aforementioned extract, which is accompanied by tachycardia, increased

TABLE 3

ARTUNDO AND SOLARI, 1933, WITH ADDITIONAL DATA

Dog	Weight Kg.	Basal Calories/sq. m./day				Pulse Rate per Min.		Dose (1) and Duration of Treatment
		Before Extract	After Extract	Absolute Increase	Percentage Increase	Before Extract	After Extract	
1	8.4	724	1190	466	64	70	92	2 g. 6 days
2	9.2	768	1362	594	77	70	105	2 g. 6 days
		873	1682	809	92	75	128	13 g. 6 days
		....	1257	510	71	....	127	2 g. 6 days
		957	1778	821	85	72	128	13 g. 6 days
3	9.	876	1056	180	20	78	85	2 g. 6 days
		751	982	231	30	72	86	12.6 g. 6 days
		952	1465	513	54	78	135	12.6 g. 6 days
B	9.8	828	1888	828	128	68	104	4 g. 8 days
		844	1709	865	102	76	110	2 g. 10 days
C	5.4	616	1344	628	101	62	100	2 g. 14 days
D	9.	722	1300	578	80	72	125	2 g. 7 days
2b	9.6	873	1692	819	93	70	140	13 g. 5 days
4	9.	738	1450	712	96	76	100	12.6 g. 6 days

(1) In g. of fresh bovine anterior pituitary prepared as alkaline extract given intraperitoneally.

pulmonary ventilation and frequently a slight rise in temperature of some tenths of a degree (3).

This metabolic increase is seen in dogs possessing thyroids (normal or hypophysectomized*) but does not occur or is very slight in thyroidecto-

*In these the thyroid hypertrophy occurred more slowly but the thyroids were atrophied at the beginning.

TABLE 4

INCREASE IN METABOLISM (IN CALS/SQ. M./DAY) PRODUCED BY DAILY INTRAPERITONEAL INJECTIONS OF 10 CC. ALKALINE ANTERIOR PITUITARY EXTRACT (1 CC.=0.2 G. FRESH LOBE) IN DOGS 6-12 KG. (HOUSSAY AND ARTUNDO, 1933)

Normals	Duration of Treatment	Thyroidectomised	Duration of Treatment	Thyroidectomised Hypophysectomised	Duration of Treatment
Calories	Days	Calories	Days	Calories	Days
+466	6	+373	6	+ 70	6
+594	6	+290	6	+262	6
+510	6	+140	6	+350	6
+180	6	− 86		− 10	6
+578	7			−170	6
+865	10			−140	6
+628	14				
+628	14				

mized animals (thyroidectomized or thyrohypophysectomized) (Table 4). The slight increase which sometimes occurs in thyroidectomized animals might be due to an impurity in the extract used or to an action of its own, which in any case is inconstant and additional (11). With purer extracts this point will possibly be cleared up.

TABLE 5

AVERAGE INCREASE IN METABOLISM PRODUCED BY 300 G. MEAT, IN CALS/SQ. M./DAY

	Absolute Increase		Percentage Increase	
	2 Hours	5 Hours	2 Hours	5 Hours
	Normal Dogs			
Artundo (1930), 6 dogs	218	396	27	48
Mazzocco (1932), 9 dogs	218	216	25	24
Houssay and Artundo (1933), 5 dogs	215	220	27	28
Average	217	271	26	32
	Hypophysectomised Dogs			
Artundo (1930), 6 dogs	273	388	34	35
Mazzocco (1932), 9 dogs	268	255	39	56
Houssay and Artundo (1933), 5 dogs	215	220	27	28
Average	261	286	34	42
	Dogs With Lesion of Tuber			
Mazzocco (1932), 5 dogs	289	362	36	45
	Thyroidectomised Dogs			
Houssay and Artundo (1933), 6 dogs	161	179	18	20
4 dogs after 6 days treatment with A. L. E.	133	150	14	16
	Thyrohypophysectomised Dogs			
Houssay and Artundo (1933), 7 dogs	144	140	19	19
4 dogs after 6 days treatment with A. L. E.	125	192	17	26

Hours after the meat feeding.

The specific dynamic action in the hypophysectomized animals is not less than in the controls, as has been shown in 20 dogs in our Institute (Artundo, 2; Mazzocco, 17; Houssay and Artundo, 12). In thyroidectomized and thyrohypophysectomized on an average it is slightly less (Houssay and Artundo, 10). Table 5 shows that the thyroid has some influence. The anterior pituitary lobe extract did not cause an increase in the specific dynamic action in the said animals.

Up to the present the basal metabolism has been determined in 22 dogs with lesions of the posterior part of the tuber cinereum, produced in 11 by caustic injections (Grafe and collaborators, 21) and in 11 by galvanic cautery (5 dogs, Mazzocco, 17; 6 dogs, Solari, unpublished results). Grafe and his collaborators found that eight of the 11 dogs in their series had lowered metabolism (average —26 per cent) and 3 were unchanged. The decrease was preceded in some cases by an initial transitory increase. Of the 11 dogs studied in this Institute six had normal metabolism and in five it was lowered. In both groups there was frequently found destruction of the posterior lobe but the anterior lobe was intact or only partially injured. The dogs with low metabolism showed great adiposity and genital atrophy. The mechanism of this lowering of the metabolism is not yet clear, but in several cases there was no epithelial atrophy in the thyroids. These points have been the object of special study by Solari, the results of which will be published later.

SUMMARY

The analysis of the influence of the hypophysis on basal metabolism in one single species (the dog) has received particular attention in our Institute (1930-1933). Hypophysectomy as a rule decreased the basal metabolism to about —16 per cent (22 of 27 dogs). This decrease is due to the anatomical (flattened epithelium, colloid more dense and devoid of vacuoles, and increased iodine content, etc.) and functional hypothyroidism induced by hypophysectomy. Dogs in which the basal metabolism did not decrease showed only a minor degree of atrophy of the thyroid epithelium.

Pancreatectomy produces either no or little increase of the basal metabolism in hypophysectomized dogs, whereas a definite increase is observed in dogs whose hypophysis has not been removed.

Hypophysectomized animals show a decrease but not a total abolition of the thyroid secretion as shown by the fact that thyroidectomy further decreases the basal metabolism (from —12 per cent when hypophysectomized only, to —22 per cent when the thyroid gland was removed in a second operation), thereby equalling the condition of animals from which the thyroid alone is removed (—24 per cent of normal).

Hypophysectomy in thyroidectomized dogs does not produce any further decrease of their basal metabolism. This shows that the hypophysis has no action of its own on the basal metabolism.

Injury of the tuber cinereum often decreases the basal metabolism (14 of 22 dogs showed such decrease) even when there is no sign of atrophy of the thyroid gland.

Alkaline extracts of the anterior lobe of the hypophysis produce hyperthyroidism and strongly increase the basal metabolism. Such an increase is wanting altogether or else is only slight in absence of the thyroid gland.

The specific dynamic action has been found normal in 20 hypophysectomized dogs studied in our Institute. This does not mean that the case must be the same in other species. In dogs lacking both hypophysis and thyroid the specific dynamic action is lower than in control animals.

The hypophysis has an indirect tonic action on metabolism through its influence in developing and maintaining the thyroid gland.

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EXHAUSTION PHENOMENON IN THYROID PRODUCED BY PITUITARY TREATMENT: HISTOLOGICAL STUDY OF RABBIT'S THYROID UNDER VARYING DEGREES OF ANTERIOR PITUITARY THERAPY

SAUL HERTZ,† M.D. AND ALFRED KRANES,§ M.D.

From the Metabolism Laboratory and Medical Services of the Massachusetts General Hospital and the Department of Medicine, Harvard Medical School

BOSTON

INTRODUCTION

In the course of a series of experiments on the relationship of the anterior pituitary body to the thyroid gland, we observed that the degree of hyperplasia obtained by prolonged treatment of rabbits with crude extracts of anterior lobe tissue did not parallel the dosage or the duration of treatment. We were struck by the appearance of the thyroid glands of animals which had received rather large doses of pituitary materials over a period of more than seven days. They showed involutional and atrophic changes which were totally unexpected since it was assumed on a priori grounds that they would show increments of hyperplasia with the increased dosages and duration of the injection periods.

PLAN OF EXPERIMENTS

Fifty rabbits of the blue bevern and Flemish giant strains were used. They ranged from 14 to 20 weeks of age. It was early evident that strain, alone, had no great influence upon the normal histology of the rabbit's thyroid. The first experiments in the series were made using saline emulsions of freshly obtained anterior pituitary glands of beef. In later experiments saline, acetic acid, and weak alkaline (NaOH) extracts were used. The latter were rendered sterile by passage through Seitz filters. Control injections were made into animals kept under the same environmental conditions as those of the experimental series. Control injections were made of heated pituitary extract, pregnancy urine extract and suspensions of fresh brain tissue of cows.

The dosages of the actively thyreotropic materials ranged from 0.1 gram of tissue in suspension to 1.0 gram; in the case of the various extracts the amounts of extract derived from these quantities of fresh tissue were used. The injections were carried out daily for periods of 2 to 28 days and were given intramuscularly. Pregnancy urine extracts were given intravenously. Paraffin sections were made and stained with haematoxylon-phloxin and eosin methylene blue.

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†Research Fellow, Harvard Medical School and Massachusetts General Hospital, Boston.
§Assistant Resident, Medical Department, Massachusetts General Hospital, Boston.

RESULTS

The histological appearances of the thyroid glands fell into three groups. Each stage is illustrated by a camera lucida drawing of a representative section.

Histology of Normal and Control Thyroids

Figure 1 illustrates the findings as seen in normal and control animals. The animal from which this thyroid was taken was an untreated reference control and received no injections. The acini were closely packed, of fairly uniform size and separated by very thin connective tissue stroma which was poor in blood vessels and not very cellular. The epithelium was low cuboidal. The colloid was plentiful in amount, stained deeply, and but

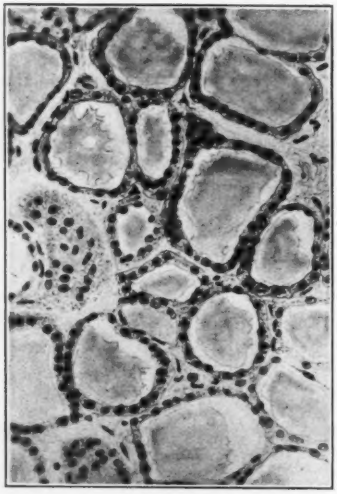

Figure 1. Camera lucida drawing of thyroid gland of rabbit No. 622, which was an untreated reference control (Normal) (x 430).

slightly vacuolated. Occasionally small areas suggesting mild degrees of hyperplasia were seen in focal areas of some of the control glands, but in none were there found the generalized changes which will be described below.

Histology of Thyroids of Animals Treated with Actively Thyreotropic Pituitary Materials

Figure 2 illustrates the type of change encountered in the thyroid glands of animals which received from 0.1 to 1.0 gram of pituitary tissue or equivalent of an active extract for from 2 to 7 days. The striking increase in cellularity, the heightened epithelium and the increased vacuolization of the colloid with its diminution in amount and depth of staining were quite characteristic of this group. In addition, the stroma showed an

increase in extent with numerous small blood vessels, increased number of nuclei and considerable mononuclear cell infiltration. Occasionally phagocytic cells were found in the colloid of hyperplastic glands.

Figure 3 illustrates the end stage of a series of involutional changes observed in animals treated for 12 to 28 days. Intermediate stages were seen between the appearances represented in Figures 2 and 3. We saw the gradual reaccumulation of colloid, the regression of the epithelium and diminution of vascularity of the glands as the treatment of the animals became more chronic until the stage seen in Figure 3 was reached. Here the strikingly distended acini, filled with a non-vacuolated colloid and composed of extremely low epithelium ("resembling endothelial lining of blood vessels") indicated a high degree of regression or involutional atrophy. Indeed, this latter picture is reminiscent of the findings in typical colloid

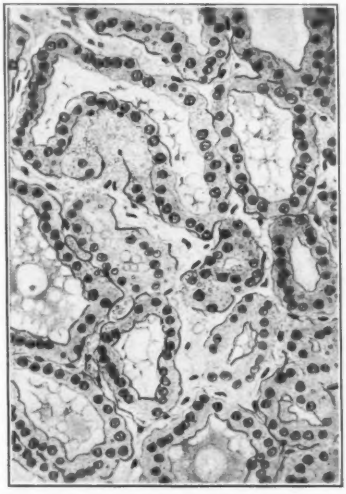

Figure 2. Camera lucida drawing of thyroid gland of rabbit No. 636, which received treatment with active thyreotropic extract for three days (Hyperplastic) (x 430).

goiter of man rather than those of the hyperfunctioning thyroid of Graves' disease.

DISCUSSION

Anderson and Collip (1) made allusion to the phenomenon herein reported as it occurred in three rats treated daily for 13 days with 4 cc. of their thyreotropic extract. They called attention to the rise in oxygen consumption which was regularly produced by the early injections; but failed to remark concerning the equally interesting, though unexpected, decrease in oxygen utilization which their animals showed on continuation of the treatment. The histological appearance of one of the rat thyroids illustrated in their paper corresponds to our stages of hyperplasia with involution.

Silberberg (2) reported his experiences in the guinea pig with anterior pituitary treatment following partial thyroidectomy. In Figure 6 of his report he illustrated a section of guinea pig thyroid taken from an animal which had received 18 days' treatment with 1½ cc. of anterior pituitary extract in daily dosage following removal of one lobe of the thyroid. The appearance illustrated was entirely comparable to that seen by Collip and Anderson. It showed evidence of hyperplasia plus a moderate degree of involution despite continuous and prolonged treatment.

A similar appearance was incidentally noted by Schockaert (3) in the duck treated by fresh suspensions of anterior pituitary of beef. In subjects treated 19 to 24 days a pathological picture similar to that of the "thyroid of man in the chronic stages of Basedow's disease" was recog-

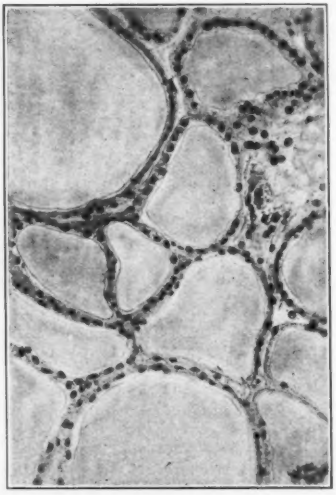

Figure 3. Camera lucida drawing of thyroid gland of rabbit No. 701, which received treatment with a proved thyreotropic extract for twenty-eight days (Involutional and atrophic) (x 430).

nized. His illustrations indicate stages of partial involution and regressive hyperplasia in these animals. No definite evidence of atrophy was seen and no metabolic data at this level of "thyroid stimulation" were recorded.

However, the extensive metabolic data collected by Szarka (4) and reported by Evans in his recent monograph indicated a primary rise in oxygen consumption in rats subjected to treatment with anterior pituitary alkaline extract. The rise was not found if the injections were preceded by total thyroidectomy. It was not eliminated by castration. The rôle of the thyroid in the metabolic rise, as independent from the gonadotropic effect of extracts, was therefore quite clear. These authors could offer no explanation for the gradual decrease of the oxygen consumption on prolongation

of the treatment. After prolonged treatment they frequently determined consumption below the initial normal levels. The degree of decrease in oxygen consumption following such treatment was comparable to that obtained following total thyroid ablation in the normal animal. Whether this decreased metabolism was maintained after cessation of the injections was not stated, but mention was made of a metabolic decrease subsequent to cessation of treatment in some of the animals which did not show a maximal metabolic decrease during the period of injections. We interpret these findings in the light of our histological data at the various stages of pituitary treatment as evidence of an exhaustion phenomenon in the thyroid as a result of the prolonged thyreotropic activity.

Friedgood (5) drew the conclusions for the guinea pig which Schockaert brought forward for the duck. He contended that anterior pituitary treatment reproduced the clinical course of the disease of exophthalmic goiter quite faithfully, indeed even to the detail of occurrence of spontaneous remissions. The anatomic illustrations given by him indicate a sequence quite similar to that seen in our own series. In discussion Friedgood suggested as an alternative explanation for the occurrence of remission the "possible exhaustion of the thyroid epithelium."

The studies of Marine (6) demonstrated the cycle of change from normal to hyperplastic to "exhaustion atrophy after spontaneous prolonged hyperplasia" and related these phenomena to the iodine content of the gland. The re-introduction by Plummer of iodine therapy in exophthalmic goiter stimulated the study by biopsy of the thyroid before and after iodine treatment. The concept of involutional thyroid change is very well summarized by Cattell (7) and Rienhoff (8) as applied to human material.

The phenomena described by the above authors are remarkably similar to those which we have observed in the rabbits under pituitary treatment and incidentally seen by other observers in similar studies. This point of view is brought forward to suggest the logical possibility of the clinical application of the thyroid exhaustion phenomenon for the induction of involution of the thyroid and of remission in human disease. The production of atrophic changes and the lowering of metabolism (Szarka) by non-surgical means seems to us to be of importance to the clinic as well.

Thyreotropic hormone is slowly becoming available in relatively pure form (Collip and others). Practical matters of therapeutic application for the above purposes will have to await carefully controlled human experiments.

Our experience in animals with respect to the gonadotropic materials of pituitary origin would indicate that none of these can be considered suitable for these purposes since even in massive dosage they are lacking in any important effect upon the thyroid.

SUMMARY

In a series of experiments on 50 rabbits varying in age from 14 to 20 weeks, groups were treated with saline emulsions and sterile (Seitz) acid and alkaline extracts of anterior pituitary glands of beef and with control injections of heated pituitary suspensions, fresh brain emulsions and pregnancy urine extracts.

Animals treated for periods of 2 to 7 days (daily intramuscular injections of 0.1 to 1.0 gram or equivalents of extracts used) showed thyroid hyperplasia. Animals treated for longer periods, i.e., 7 to 12 days, showed early regressive and involutional changes with remnants of hyperplasia in their thyroids. The thyroids of animals treated for from 12 to 28 days showed increasing degrees of involution and finally atrophy of the epithelium and marked colloid storage. Control extracts are without effect.

The above sequence is interpreted as indicative of an exhaustion phenomenon in the thyroid as a result of prolonged thyreotropic action. Metabolic evidence in support of this hypothesis and its possible clinical application are briefly discussed.

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PERIODICALS ON ENDOCRINOLOGY OF SEX

WILLIAM F. MENGERT, M.D.

Gynecean Hospital Institute of Gynecologic Research, School of Medicine, University of Pennsylvania

PHILADELPHIA

The subject of the physiology of the ductless glands relating to sex and sex function is so complex that the average physician is staggered by the number of the periodicals which must be read in order to gain any sort of orderly knowledge. The appearance of "Sex and Internal Secretions" (1), edited by Allen and written by 22 investigators, each prominent in his special subdivision of the subject, has done much to make the acquisition of a basic understanding of sex hormonology easier. However, the subject is in a stage of flux, discoveries are constantly being reported and unless one keeps abreast of the articles in current journals he is soon in as hopeless a state as before. The average man, not working in the field, is too busy to read all the medical journals which may have occasional articles pertaining to sex endocrinology. Therefore, he wants to know what journals should be read in order to maintain a reasonable idea of current progress.

TABLE I

JOURNALS PUBLISHING THE MAJORITY OF THE ARTICLES REFFERRED TO IN "SEX AND INTERNAL SECRETIONS"

Journal	Number of References to Each Journal	Cumulative Total of References	
		Number	Per Cent
1. American Journal of Physiology	169	169	6.8
2. Comptes rendus des séances et mémoires de la Société de Biologie	142	311	12.6
3. Proceedings of the Society for Experimental Biology and Medicine	125	436	17.6
4. Anatomical Record	116	552	22.3
5. American Journal of Anatomy	106	658	26.6
6. Journal of Experimental Zoology	99	757	30.6
7. Archiv für Gynäkologie	75	832	33.6
8. Endocrinology	61	893	36.1
9. Klinische Wochenschrift	54	947	38.3
10. Proceedings of the Royal Society of London	52	999	40.4
11. Zentralblatt für Gynäkologie	51	1050	42.5
12. Journal of the American Medical Association	49	1099	44.5
13. Journal of Physiology	41	1140	46.1
14. Biological Bulletin of the Marine Biological Laboratory	38	1178	47.6
15. Johns Hopkins Hospital Bulletin	35	1213	49.0
16. British Journal of Experimental Biology	33	1246	50.4
17. Carnegie Institute of Washington Publications	33	1279	51.7
18. Archiv für die gesamte Physiologie des Menschen und der Tiere (Pflüger's)	32	1311	53.1
19. Archiv für Entwickelungsmechanik der Organismen	32	1343	54.3
20. American Naturalist	28	1371	55.5
315 other journals	1103	2474	100.0

The table shows the 20 journals most frequently cited, the number of references to each and cumulative totals and percentages. For example: The first 10 journals listed published 999 articles, or 40.4 per cent of the total of the 2474 references appearing in "Sex and Internal Secretions."

In an attempt to answer this question, all the references in Allen, "Sex and Internal Secretions," were analyzed. After excluding references to books, theses, et cetera, there remained 2474 references to 335 different periodicals. Table I records the 20 journals most frequently cited. It will be seen at once that 55.5 per cent of the 2474 articles appeared in these 20 journals.

When the whole list of 335 journals is considered, the law of diminishing returns is strikingly illustrated, and a curve (Figure 1) results which

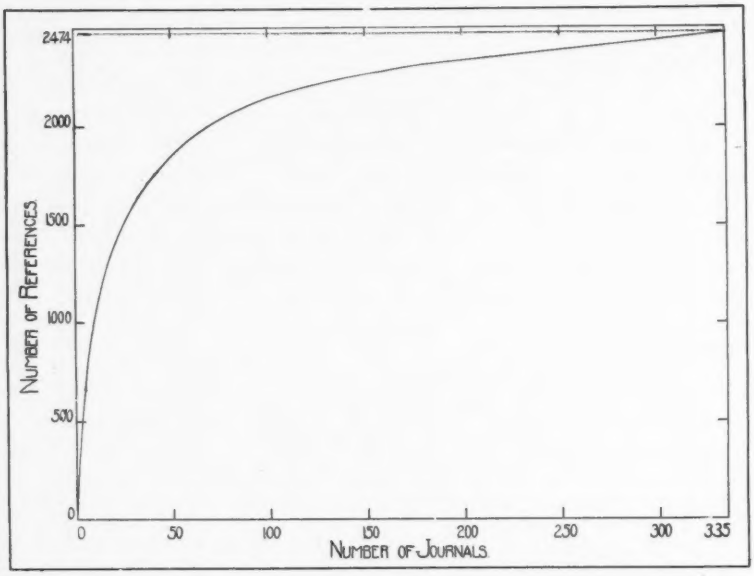

FIGURE 1

Presents graphic representation of the law of diminishing returns as applied to the references appearing in "Sex and Internal Secretions." A small number of journals published the majority of the articles quoted. As the number of journals is increased, the number of additional articles published in each decrease enormously.

is similar to that published by Jenkins (2) in an analysis of journals and references appearing in the Journal of the American Medical Association, the British Medical Journal and the Klinische Wochenschrift. Though 55.5 per cent of all the articles referred to in Allen's book may be found in 20 journals, it is necessary to read 315 more journals in order to find the remaining 44.5 per cent.

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Book Reviews

WHAT WE ARE AND WHY. Laurence H. Mayer in collaboration with Arthur D. Welton. P. 340. Sears Publishing Co., Inc., N. Y. 1933.

This book might be fairly characterized as a treatment of the sociology of the internal secretions. Most books on endocrinology discuss in an impersonal way the phenomena resulting from aberrations of hormone secretion, largely neglecting what is to the individual the most important consideration, the significance of the aberrations in his own life picture.

The technical endocrinology is none too sound in that the reportorial device of substituting half-truths for full statements is not infrequently used. The picture that is drawn is on the whole, however, not seriously inconsistent with the detailed facts though one regrets such facile generalizations as that the pituitary determines courage and fortitude. To a very considerable extent the book might be characterized as a collection of picturesque data vivaciously presented.

Of special interest are the discussions of the infantilist as a reformer. The author lays much stress on mumps as a cause of infantilism. The tragic possibilities of obesity are also graphically presented. The book on the whole can be recommended to those who know enough endocrinology not to be misled and who wish to view the subject in its social setting.

SEX AND INTERNAL SECRETIONS. Ed. Edgar Allen. P. 951. The Williams & Wilkins Company, Baltimore, Md. 1932.

For the past decade a program of research on fundamental problems of sex has been carried on under the auspices of the Division of Medical Sciences of the National Research Council. At the end of the decade Professor Edgar Allen was invited to organize a cooperative survey of recent advances in research on internal secretions in relation to sex. This book embodies the contributions that were made by twenty-one members of the participating group.

The book represents an authoritative and skillful presentation of much of the fundamental information now available. The authors are specialists in their respective fields and the book as a whole is correspondingly somewhat technical. The chapters include a general biological introduction; interrelationship of genic and endocrine factors in sex; genetics of sex in Drosophila; embryological foundations of sex in vertebrates; sex deviations, inversions and parabiosis; metabolism in sex; biology of the testis; biochemistry and assay of testis hormones; ovarian follicular hormone—animal reactions; biochemistry of the follicular hormone; physiology of the corpus luteum; the mammary glands; plumage tests in birds; ovulation and transport and viability of ova and sperm in the female genital tract; effect on the reproductive system of ablation and transplantation of the anterior hypophysis; effects of extracts of the anterior pituitary and similar active principles of blood and urine; anterior pituitary changes referable to the reproductive hormones, and the influence of the thyroid and the adrenals on genital function; sexual drive; and endocrine function of sex disorders in man. The book concludes with an index of authors and index of subjects. Each chapter includes a well-selected bibliography.

Altogether, the book "brings together under one cover a vast fund of information and data concerning the most important and valuable contributions to the study of internal secretion as it relates to problems of sex."

To a large extent the work deals with the fundamentals of knowledge in this field rather than to clinical applications of this knowledge. Hence its appeal is to the student of endocrinology rather than to the applied endocrinologist. To the latter, however, it is invaluable in affording direct access to the basic information upon which sound application necessarily rests.

Abstract Department

Bi-lateral suprarenal hemorrhage and death in epilepsy. Damon, L. A., Psychiatric Quart. **6:** 438. 1932. Abst., J. Nerv. & Ment. Dis. **78:** 190.

A case of bi-lateral suprarenal hemorrhage occurring in an epileptic, thirty-five years old, is reported. The patient was suddenly seized with cramp-like pains in the abdomen, diarrhoea and symptoms of shock. There was complete collapse, marked drop in blood pressure and failure of the circulation with rapid death within 15 hours from the onset. Autopsy showed marked edema of the peritoneum with extensive hemorrhages into both suprarenal bodies. Histologically the normal cellular relations were completely destroyed and replaced by extravasated red blood cells. Both medulla and cortex were equally affected. The rareness of this condition is emphasized by the fact that only 20 cases were reported in the literature of the past 20 years. Of these, three occurred in epileptics and this high percentage is sufficient to place epilepsy as one of the predisposing causes of this unusual condition.

Use of suprarenal cortex extract in treatment of bronchial asthma. Fineman, A. H., J. Allergy, **4:** 182. 1933. Abst., J. A. M. A. **101:** 243.

Fineman treated four patients who had severe asthma (three protein sensitive and one non-sensitive), for a period of from one to 27 months, with little or no improvement. He then used suprarenal cortex extract, beginning with a dosage of 0.5 cc. and increasing it up to 4 cc. Injections were given three or four times weekly during the first month and once or twice weekly thereafter. Subcutaneous and, intramuscular injections were administered in each case. Two patients received treatment for four months, one for three months and one for six weeks. One patient showed marked improvement in asthma, one moderate, one slight and one no improvement. In three of the patients a decided increase in strength and appetite was noted, with an average gain in weight of 4½ pounds (2 Kg.). The general condition of the patients was definitely improved. No appreciable change in blood pressure was noted during or at the end of the course of treatment. No influence on the pulse rate was observed. The author believes that the results obtained with the suprarenal cortex in the treatment of these four patients warrant its further trial in a larger series of cases, employing larger dosage and utilizing, if necessary, the intravenous route.

The effect of dehydration on adrenal secretion and its relation to shock. Freeman, N. E., R. S. Morison and M. E. MacK. Sawyer, Am. J. Physiol. **104:** 628. 1933.

In cats (number not stated) acute dehydration caused an increase in the rate of the denervated heart as well as contraction of the nictitating membrane. No increase in the rate of the denervated heart accompanied dehydration when the adrenals were inactivated. Reasons are given for regarding asphyxia, resulting from a diminished blood flow, as the means by which dehydration stimulates secretion of adrenine. No increase occurred in the total volume of red blood corpuscles circulating during dehydration when the spleen and the adrenals were denervated. Activity of the sympathetic nervous system is invoked to explain certain phenomena noted in clinical or experimental dehydration, such as the rapid heart rate, the decreased clotting time of the blood, and the higher level of blood sugar. The similarity between traumatic shock and dehydration is stressed in that both conditions are characterized by vasoconstriction from activity of the sympathetic nervous system and a slowing of the blood flow which leads to a reduction in the volume of the circulating blood.—R. G. H.

The use of cortin following removal of a large adrenal tumor. Prather, G. C., New England J. Med. **208:** 872. 1933.

A hypernephroma, weighing 2.5 lbs., was removed from a woman, 42 years old. The blood pressure post-operatively sank to 68/48, in spite of therapeutic measures. "Cortin" injections over a period of 48 hours produced a gradual rise in blood pressure to 110. The patient was discharged and lived 2½ months in active life without further medication.—J. C. D.

Adrenalinemia and adrenalinuria (Adrenalinemia e Adrenalinuria). Viale, G., Rev. sud-am. endocrinol. **16:** 387. 1933.

Adrenaline may be detected in blood, serum or urine by a red color developed after the addition of a drop of the saturated solutions of mercuric chloride, sulfanilic acid and potassium iodate, followed by short heating. The reaction is prevented by formaldehyde; 80 parts of the latter inactivate one part of adrenaline. By the use of standardized formaldehyde solution, a quantitative method for adrenaline determination is developed, which is sensitive to very high degrees of dilution. The concentration of adrenaline in dog serum is 1:500000, in the whole blood 1:400000. Tests on hemolyzed and washed red corpuscles proved that the erythrocytes carry more adrenaline than the serum. Adrenalectomy in dogs causes only a slight reduction of the adrenaline in the blood. Healthy individuals excrete it in the urine. Persons with high blood pressure show high values in the urine. It may be absent in cases of low blood pressure (105-110 mm. Hg. as maximum). Rabbits exposed to high O pressure show adrenalinuria and hyperglucemia.—A. E. Meyer.

Cortical proliferation in the mouse suprarenal after peptone. Whitehead, R., Brit. J. Exper. Path. **13:** 200. 1932.

The incidence of mitosis in the suprarenal cortex was studied in 96 mice after intraperitoneal injection of Witte's peptone. Mitosis first became appreciable 56 hours after injection, reaching the maximal between 71 and 83 hours thereafter, and declining at 97 hours. Mitoses were most numerous in the outer part of the cortex, spiremes far outnumbering asters. Mitosis was as a rule most active in mice showing the least departure from the normal temperature, general condition and weight. Since no lesions were seen in any suprarenal, the proliferation is held to be "functional" as distinct from "regenerative."—Author's Abst.

Nervous organic disease (Über nervöse Organkrankheiten). Josefson, A., Acta med. Scandinav. **75:** 541. 1931.

Josefson has reported the case of a man, aged 32 years, who presented the following clinical features: emaciation, anorexia, weakness, mild somnolence, a brief phase of polyuria and polydipsia, dryness of mouth and throat, feelings of cold, falling out of hair of scalp and loss of body hair, changes in nails and teeth, loss of libido and potentia, dizziness, depression, occasional headaches, achylia gastrica, retarded basal metabolic rate (minus 23%), arterial hypotension (85/60), and hypoglycemia. At the autopsy a small tumor of hazel nut size was found in the diencephalon in the region of the mammillary bodies. The viscera were of small size and the endocrine glands especially were atrophic, including the hypophysis which, however, was normal on histological examination. The ribs were thin and fragile. It is of great interest that so many symptoms and signs usually attributed to primary endocrine dyscrasies seem in this case to be due to a small lesion in that part of the brain, the site of the most important centers of autonomic nerve impulses. One may conjecture concerning a possible secondary rôle played by the hormones.

—From T. P. Sprunt, Ann. Int. Med. **7:** 261. 1933.

The action of the pituitary sex hormone on some endocrine glands (pancreas, adrenals, hypophysis, thyroid) after ligature of the deferent vessels (L'ozione dell' ormone sessuale ipofisario su alcune ghiandole endocrine [pancreas, surrenali, ipofisi, tiroide] dopo legature dei deferenti). Lucarelli, G., Biochem. e. terap. sper. **20:** 10. 1933. Abst., Chem. Absts. **27:** 2722.

Prolan caused in the anterior lobe of the pituitary hypertrophy and hyperplasia and the appearance of cells of the characteristics of so-called "pregnancy cells." Pancreas, thyroid and adrenals did not show any change.

Erythremia; therapeutic suggestion. Morris, R. S., J. A. M. A. **101:** 200. 1933. Abst., A. M. A.

As pernicious anemia appears to be due to a lack of secretion of addisin, the author states that it is theoretically possible that erythremia may be the result of hypersecretion of addisin or of hypersusceptibility of the marrow to it. A similar hormone theory has been advanced by Hurst and by Tuchfeld. In a

patient with erythremia, having 8.9 million red cells, addisin derived from 1,250 cc. of the gastric contents of swine was injected intramuscularly. On the fifth day following the injection, the reticulocytes, which had been in the neighborhood of 1%, rose to 2.5%, or from 89,000 to 212,000 per cubic millimeter. Coincident with this reaction, an occasional normoblast was found in the blood and erythrocytes containing minute nuclear particles, which were absent or nearly so (270 per cubic millimeter), rose to a maximum of 14,700 per cubic millimeter on the sixth day, followed by a rapid fall. On the ninth day after the injection, a differential count showed 1% myelocytes. These results indicate clearly a response of the bone marrow to stimulation by addisin, despite the polycythemia. Examination of the sources of hematopoietic substances effective in pernicious anemia discloses a high urine content (liver, kidney, stomach, nucleic acid). Should the diseases pernicious anemia and erythremia represent in reality an addisinism and hyperaddisinism, as seems theoretically possible, there would seem to be the possibility of controlling erythremia by means of dietary measures. For this purpose the author suggests a low purine diet continued over a long period of time, with careful study of the blood.

Three cases of sclerotic blue and the endocrines (Sur trois observations de sclérotiques bleues avec troubles endocriniens). Nilus, F., Rev. franç. d'endocrinol. **9**: 33. 1931.

During his military service the author observed three blue sclerotics out of a considerable number of civilians and 1800 recruits. Case one presented an intermittent blue aspect of the sclera coincidental with periods of vasomotor reactions and trembling of the limbs. In several of these crises there occurred ligamentary laxity, dental caries and ocular and auditory deficiency. There was no hereditary or acquired syphilis. Case two showed blue sclera with osteopsathyrosis in a hereditary syphilitic whose mother and brother had the same symptoms. Case three presented blue sclera with thyroid and parathyroid disturbance in three successive generations and with no symptoms of syphilis.
—I. B.

Influence of sex hormones on creatine metabolism (Über den Einfluss der Sexualhormone auf den Kreatinstoffwechsel). Bühler, F., Ztschr. f. d. ges. exper. Med. **86**: 638. 1933. Abst., J. A. M. A. **100**: 1377.

Bühler studied the creatine metabolism and the decomposition of creatine by hormones following intravenous injection of 500 mg. of creatine. His observations were made on persons in whom sexual function had ceased, on patients with incretory disturbances, on two patients with disorders of the muscles, and on children before puberty. The parenterally administered creatine was eliminated always unchanged in form but not always in quantity. Following hormone administration, but under otherwise unchanged conditions, a considerable decomposition of the creatine became manifest. However, in prepuberal children this action of the hormones was absent, for the children still eliminated the largest portion of the creatine. The male sex hormone influenced creatine decomposition only in men and the female sex hormone only in women. In the reverse condition the decomposition was inhibited. This proves that the action of the sex hormones on creatine exchange is sex specific. The author also describes a new method for the determination of the creatine-creatinine values of the urine. This method employs the step photometer of Pulfrich. The superiority of this method over other colorimetric tests is that it makes the use of a comparative solution unnecessary and that the reading, which is based on a standard curve, is simple.

Inhibition of ovulation in rabbit by folliculin (Inhibición de la ovulación en la coneja por la foliculina). del Castillo, E. B., Rev. Soc. argent. de biol. **8**: 591. 1932.

Three adult female rabbits received subcutaneously 10 rat units of folliculin daily for 31 days. They were then placed, together with a control, with a male rabbit for 24 hours. Spermatozoa were found in the vaginas. Twenty-four hours later they were killed and the ovaries examined. The control had several bloody points on the ovary, which weighed 500 mg., 5 active corpora lutea were found in histological examination. The treated animals had small ovaries (19.4-32-41 mg.) and no ruptured follicles nor corpora lutea. The pituitaries showed no significant differences in weight.—J. T. L.

The hypertrophy of the ovary in relation to the ovarian hormone. Emery, F. E., Proc. Am. Physiol. Soc. P. 30. 1933.

The hypertrophy of the remaining ovary after unilateral ovariotomy is well known. The cause of this hypertrophy is thought to be related to the pituitary gland; however, implants have failed to show the pituitaries from rats with one ovary were more potent than normal. Immediately after one ovary is removed the amount of ovarian hormone is reduced by one-half and this may play a part in starting the hypertrophy in the remaining ovary. Theelin (1 to 5 R.U. daily) was, therefore, given unilateral ovariectomized rats but this did not prevent the hypertrophy of the remaining ovary. Whatever the cause of the hypertrophy may be, it is not diminished by moderate doses of theelin.—Author's Abst.

Comparative studies of gonad-stimulating hormones; influence of length of period of administration of certain extracts. Fluhmann, C. F., Proc. Soc. Exper. Biol. & Med. **30**: 1014. 1933.

The administration of a known total dose of an ovary-stimulating pregnancy blood extract over periods of 10, 15, or 20 days produced a much greater increase in ovarian and uterine weights of immature rats than when the same total dose was given in 5 days. The opposite result was obtained with acid extracts of sheep anterior pituitary glands, as the injection of a known dose in 5 days produced a greater increase in ovarian weight than when the administration of the same total dose was spread out over periods of 10, 15, or 20 days.
—Author's Summary.

Metabolism of women during the reproductive cycle; nitrogen utilization. Hunscher, Helen A., Eva Donelson, Betty Nims, Fanny Kenyon and Icie G. Macy, J. Biol. Chem. **99**: 507. 1933. Abst., Chem. Absts. **27**: 1033.

The observations reported in this investigation in combination with the existing data from the literature are a survey of the present knowledge concerning the relation of nitrogen retention in women to the demands of the reproductive cycle. The records indicate that the maternal body retains in pregnancy a considerable excess of nitrogen beyond that required for the fetus and its adnexa. After parturition there is a loss which persists over the first two weeks or more of the puerperal period. There is evidence that the mother has the ability to maintain nitrogen equilibrium during established lactation and post-lactation. In short, the nitrogen metabolic balance studies although of brief duration would indicate that under favorable circumstances the reproductive cycle is a period of nitrogen acquisition for the mother.

Masculinization of the external genitalia of female guinea pigs by injection of male hormone (Ueber die Maskulinisierung der äussern Genitalien von weiblichen Meerschweinchen nach Injection von männlichem Hormon). de Jongh, S. E. and J. D. Mulder, Endokrinologie, **11**: 161. 1932.

Two daily injections of one B.U. of testis-hormone into mature female guinea-pigs for a period of 1½ months brought about an increase in the size of the clitoris and its assumption of a penis-like shape and texture. Similar results were obtained by substituting a female hormone preparation (menformon) for the testis hormone, as well as by injecting the animals simultaneously with both testis hormone and menformon. The enlargement of the clitoris is in some cases merely palpable whereas in others it becomes externally perceptible. Moreover, the enlarged clitoris develops a pair of nodular outgrowths which apparently correspond to the spines of the penis of the male guinea-pig, and whose rudiments, in the form of papillae, were found on the clitoris of normal uninjected female guinea-pigs. Pregnancy, evidently through the influence of an increased production and release of oestrin, likewise stimulates the development of these nodular processes.—M. Zalesky.

The effect of anterior hypophysis on conception and pregnancy in the guinea pig. Kelly, G. L., Surg. Gynec. & Obst. **57**: 216. 1933.

Eleven guinea pigs were injected with the expressed juice of 3 to 10 beef hypophyses. Of the 8 animals that survived all conceived. Four pregnant animals each received the juice of 3 to 12 glands. All aborted and then died. Eight were injected beginning on the day of impregnation with 5 to 10 cc. of

extract of pregnancy urine (250-500 units). Six conceived, two did not. All survived. Fourteen pregnant animals each received 5-27 cc. of urine extract. Eleven aborted, one delivered her young at term and two died. The extracts then did not prevent conception but commonly did cause abortion.—R. G. H.

The pathology of hirsutism and virility (Beitrag zur Pathologie des Hirsutismus und Virilismus). Kovacs, F., Monatschr. f. Geburtsch. u. Gynäk. **91:** 65. 1932. Abst., Am. J. Obst. & Gynec. **26:** 141.

Kovacs reports a rare case in which a woman developed among other masculine characteristics a marked increase of hair all over the body and especially a full-grown beard This is the first recorded case in which the removal of the ovaries in a patient who did not have a suprarenal tumor resulted in hirsutism. The author draws a practical conclusion from this case, namely, that the removal of both ovaries may in certain cases not only lead to the usual symptoms of the menopause but it may also result in severe somatic and biologic disturbances. Therefore in a deliberation between surgical and radiation castration we should take into consideration not only the patient's age, family and relationships, etc., but also where possible the constitutional type of the individual with special reference to the intersexual type and latent heterosexual peculiarities.

Increased stimulation of immature rat ovaries by combined injections of prolan and hypophyseal sex hormone. Leonard, S. L., Proc. Soc. Exper. Biol. & Med. **30:** 403. 1932.

Experiments are reported on 10 litters (53 animals). When pregnancy urine extract and a hypophyseal sex hormone fraction were injected simultaneously into sexually immature female rats, the weights of the ovaries produced ranged from 20 to 466% above expectation of additive effects from the two substances acting individually. The average excess was 142%. The water soluble fraction of a pyridine extract of sheep anterior pituitary was the hypophyseal extract used and was free of growth hormone when tested on dwarf mice and hypophysectomized rats. The increased stimulation produced by the combined injection cannot be explained on the basis of conversion of a growth hormone factor as is believed by other workers. Furthermore, a placental extract may be substituted for the pregnancy urine extract to obtain similar results.

Author's Abst.

The skin as a hormone bearer during pregnancy (Die Haut als Hormonträger in der Schwangerschaft). Loeser, A., Zentralbl. f. Gynäk. **56:** 1155. 1932. Abst., Am. J. Obst. & Gynec. **26:** 137.

Skin was obtained from 14 pregnant women, either during laparotomy for intercurrent disease or during cesarean section at term. It was denuded of underlying tissue, and pieces not less than 10 by 10 mm., weighing at least 100 mg., were implanted under the skin of infantile rats, castrated infantile and castrated adult rats. The Allen-Doisy test was negative in every instance, however, ripe follicles, estrus, and (when large pieces of skin were used) corpus luteum were found. The greatest amount of hormone in the skin was ascertained in early pregnancy (four to six weeks), less was found at the 4-5 month period, and the least amount in skin of patients at term. At least five times as much urine as skin (by weight) is necessary to give a reaction. The author realizes that lymph and serum are implanted with the skin and that this constitutes an objection to the study. The question was raised as to whether the concentration of hormone in the skin has anything to do with skin pigmentation during pregnancy, but skin taken from the linea nigra and from other parts of the abdomial wall of the same individual did not give any appreciable difference in reaction.

The endocrine influence on the male sex organs. Lower, N. E., New England J. Med. **208:** 878. 1933.

In rats, castration followed by injections of hypophyseal extract or testicular extract results in atrophy of the prostate and seminal vesicles. Hypophyseal extract injected into intact rats or into rats treated with x-ray, so that the tubular epithelium is destroyed and the interstitial cells left uninjured, produces marked prostatic enlargement. Injections of male sex hormone from the urine prepared by the method of McCullagh also produces prostatic enlargements in rats,

whether the gonads are intact or not. These injections do not, however, restore the enlarged hypophysis or adrenals of castrated males to their normal size. Injections of testicular extract after castration will prevent enlargement of adrenals and hypophysis. The above experiments together with other clinical and laboratory observations lead the author to assume that the testis produces two hormones. One is an inhibitor of the hypophysis which is produced by the tubular epithelium and another which is produced by the interstitial cells and which controls the secondary sex characters, including the size of the prostate. In man, tubular atrophy is followed by increased activity of the hypophysis, overproduction of hormone by the interstitial cells and, therefore, by prostatic enlargement. In dealing with prostatic hypertrophy some method of reducing the output from the interstitial cells should be considered. The favorable influence of castration on the prostate in certain cases favors this view.—J. C. D.

Creatinuria and ovarian function (Kreatinurie und Ovarialfunktion). Remen, L., Ztschr. f. d. ges. exper. Med. **81**: 223. 1932.

Ten women who were past the climacteric were placed on a meat-free diet. The amounts of creatin in 24-hour urine samples were determined. Then 500 mgm. of creatine was injected intravenously. The creatine output on the following day was increased, varying from 91 to 216 mgm., the average being 128 mgm. Four women were injected with Menformon—2300 units over a period of ten days. Then (500 mgm.) creatine was injected intravenously. One of the patients felt every influence of the Menformon. Two of the cases showed an increased output of creatine but not as high as when no Menformon was injected. From his results the author believes that there is a relationship between ovarian activity and creatine metabolism.—E. L.

Clinical trials with the so-called female sex hormone. Rock, J., New England J. Med. **208**: 362. 1933.

The author discusses our newer knowledge of the relations between Prolan A or luteinizing hormone from the urine of pregnancy, estrin from the Graafian follicle, and progestin from the corpus luteum. In certain cases of threatened miscarriage, the estrin content of the blood was very high. Luteinizing hormone, when injected, increased the excretion of estrin and seemed helpful. In seven of 10 cases of amenorrhea favorable results were obtained by combined treatment with estrin and luteinizing substance. Luteinizing substance helped in 13 of 15 cases of menorrhagia and allied conditions. These results as far as they go are in line with our present theories but the author warns that any promiscuous or over-enthusiastic application of these preparations will lead to disappointment.—J. C. D.

The production of deciduomata in immature rats by pregnancy urine treatment. Shelesnyak, M. C., Am. J. Physiol. **104**: 693. 1933.

An investigation was made of the functional capacity of pregnancy-urine induced corpora lutea in the infantile rat. The production of deciduomata in the traumatized uteri of urine treated immature rats was employed as a test for functional activity of the corpora. One hundred and forty-four (144) infantile female rats were treated daily with various amounts of pregnancy urine extract (Follutein, Squibb) ranging from 0.25 to 20.0 Z-A units per day. The uteri of animals were stimulated by thread loops on different days of treatment from the 3rd to 22nd. Autopsy was performed five days after the traumatization. The results (75.6% showed decidual responses) demonstrated the capacity of pregnancy urine for inducing functional corpora lutea in the infantile rat. A periodicity of the frequency of decidual responses over date of uterine stimulation was noted.—Author's Abst.

The production of deciduomata in spayed immature rats after oestrin and progestin treatment. Shelesnyak, M. C., Anat. Rec. **56**: 211. 1933.

In order to test the physiological capacity of the infantile uterus to form deciduomata, a series of 56 immature rats were spayed and treated with varying amounts (from 4 to 100 r.u.) of oestrin (Amniotin, Squibb) for four days. After the preliminary injections of oestrin, alcohol extracts of hog corpora lutea (from 4 to 84 grams equivalent of fresh tissue) was administered for eight days. The uteri were stimulated by modified silk thread loops on the fourth or fifth

day of progestin treatment. The results show that such treatment develops a trauma-sensitive endometrium, and decidual growths are formed. Although 52% of the animals (each of which received a different dosage of oestrin and progestin) show some response, macroscopic growths were few (6) and limited to animals which were given the lesser quantities of substances.—Author's Abst.

The effect of amniotin on the basal metabolism of rats and rabbits. Sherwood, T. C., M. Savage and J. F. Hall, Am. J. Physiol. **105**: 241. 1933.

A commercial preparation of ovarian hormone (amniotin) showing the typical oestrogenic action on normal and ovariectomized animals induced a decrease of 13 to 42% in basal metabolism when injected into 15 ovariectomized and 15 intact animals. In rabbits, the basal metabolism of which had increased 30% or more from thyroid feeding, we were able to induce a 37% decrease in basal metabolism within three days following the injection of 100-800 R.U. of amniotin. The results obtained would indicate an indirect or direct relation of the ovarian and thyroid function, possibly by way of the hypophysis.—Authors' Abst.

Dysfunctional uterine bleeding; results in treatment with extracts of the urine of pregnant women. Smith, G. V. S. and J. Rock, Surg., Gynec. & Obst. **57**: 100. 1933.

Antuitrin S, an extract of the urine of pregnant women, was administered to 56 patients with dysfunctional uterine bleeding with the following gross results: cured, 28; benefited, 22; unrelieved, 6. The cessation of bleeding accompanied treatment so often and in many so rapidly as to leave little doubt of the specificity of the hormone, especially considering the variable potency of the preparations supplied. A limited number of laboratory findings have suggested a clue concerning the mechanism of this hormone's therapeutic action, namely, the possibility of a direct action on a hypophyseal hormone.

—Authors' Summary.

Hormone diagnosis of viability of pregnancy. Spielman, F., M. A. Goldberger and R. T. Frank, J. A. M. A. **101**: 266. 1933. Abst., A. M. A.

The authors studied 33 pregnancy cases in which missed abortion was suspected or expected from the hormonal aspect in order to determine the relationship between the female sex hormone of the blood and the prepituitary hormone of the urine and fetal life or death. The Frank-Goldberger method was used in the blood studies, and either the Aschheim-Zondek or the Friedman test in the urine studies. A negative female sex hormone reaction was obtained when the fetus was dead (23 cases) and a positive reaction when the fetus was alive (eight cases). The results here were 100% correct in 11 cases. A negative pregnancy reaction was obtained when the fetus was dead, and 10 gave positive reactions in spite of dead fetuses (approximately 50% correct). The female sex hormone blood determination has proved itself in the authors' series an absolute indicator of whether a fetus is alive or dead. The urine pregnancy test is of value only when the reaction is negative. The presence or absence of the hormones depends on the degree of involution of the placenta and its attachment to the uterine wall.

Arrhenoblastoma of the ovary. Taylor, J. M., S. J. Wolfermann and F. Krock, Surg., Gynec. & Obst. **56**: 1040. 1933.

The authors review the literature that reports 26 cases of arrhenoblastoma of the ovary and add a description of a patient personally studied. She was a white girl of 18 who complained of severe abdominal pain, cough, fever, and pain in the chest. Menstruation began at 13 and suddenly ceased at 14. On admission four years later she showed bushy eye-brows and a vigorous beard. The pubic hair was of the masculine type and the clitoris thrice the normal size. Operation disclosed a cystic ovarian tumor from which 4000 cc. of fluid was aspirated. It was intraligamentary and arose from the region of the left ovary. The right ovary was about half the normal size and devoid of graafian follicles. The uterus was one-third the normal size. After removal of the ovary menstruation was resumed and other manifestations of femininity appeared such as growth of the breasts. The hair growth on the face became much less profuse. Evidence is cited that the primary tumor originated from anlagen in the rete of residual undifferentiated cells corresponding to the tes-

ticular interstitial cells of the normal male. When the masculinizing activity of these was removed the patient reverted toward the feminine habitus. The endocrinological aspects of the disorder are discussed at some length.—R. G. H.

Physiologic action of folliculin upon the pregnant (Beitrag zur physiologischen Wirkung des Follikulins auf den schwangeren Uterus). Tschaikowsky, W. K., Zentralbl. f. Gynäk. **56**: 295. 1932. Abst., Am. J. Obst. & Gynec. **26**: 142.

The author reviews several facts concerning the hormones of pregnancy: (a) the folliculin content of the serum rises toward the end of pregnancy; (b) the prolan content does not rise and even falls during the last three months; (c) corpus luteum is in regression at the end of pregnancy and inhibits the sensitiveness of the uterus for posterior pituitary. Twenty-two white mice in the second half of pregnancy were injected with 2.5 cc. of a lipoid emulsion of folliculin daily for several days. Two or three days after the injections were begun energetic contractions of the uterine horns appeared within 20 to 25 minutes after the previous injection. The pains which came at three to five-minute intervals and lasted on to one and one-half minutes, slowly disappeared two or three hours later. Usually the mice aborted three to four days after injection, and the nearer they were to the end of pregnancy the more energetic were the uterine contractions. The following conclusions were drawn: Folliculin sensitizes the uterus for the action of posterior pituitary hormone. It raises the restraining action of corpus luteum on posterior pituitary. The decrease of prolan production at the end of pregnancy causes diminished luteinization of the ovaries and therefore promotes the supremacy of folliculin over corpus luteum. Therefore, weak pains during labor are an expression of an overproduction of corpus luteum or an insufficient production of folliculin.

Observations on the accuracy of the rabbit ovulation test for pregnancy. Ware, H. H., Jr., and R. J. Main, J. Lab. & Clin. Med. **18**: 254. 1932.

The authors tested 150 patients for suspected pregnancy with the rabbit ovulation test and later established the diagnosis clinically in 100 of these. This test proved to be accurate with but one possible exception. The rabbit ovulation test is of particular advantage in the diagnosis of hydatidiform mole, missed abortion, ectopic pregnancies, uterine fibroids, menopause and tubo-ovarian abscesses. The earliest pregnancy giving a positive result was six days after the menstrual period was due. Following delivery a negative result was obtained in from 24 to 72 hours.—I. B.

The interrelationship between ovarian follicle cysts, hyperplasia of the endometrium, and fibromyomata; a possible etiology of uterine fibroids. Witherspoon, J. T., Surg., Gynec. & Obst. **56**: 1026. 1933.

An hypothesis is advanced to suggest that the unopposed action of estrin on the myometrium, if prolonged sufficiently, would result in fibromyomatous growths. Twenty-six cases of hyperplasia of the endometrium, in which operation was done and diagnosis as such made from microscopic study, and in which a second operation was performed for fibromyomata after an approximate interval of four years and four months, are analyzed. One hundred and twenty-four cases of fibromyomata, diagnosed microscopically, are offered with their associated ovarian and endometrial findings, as presenting added evidence in support of a cause and effect relationship between ovarian follicle cystic formation, hyperplasia of the endometrium, and fibromyomata of the uterus. An hypothetical conclusion is advanced that the unopposed action of estrin on the uterus results: (1) in immediate endometrial changes, characterized by hyperplasia, and (2) in more latent myometrial pathology in the nature of fibromyomatous growths.

Cause of onset of labor; an hormonal investigation. Witherspoon, J. T., Proc. Soc. Exper. Biol. & Med. **30**: 1367. 1933.

Theelin or ovarian follicular fluid was administered to 12 pregnant women at full term. In only two cases did labor occur within 36 hours. The same hormone, in the form of amniotin or progynon was administered to 30 full-term pregnant women. Seven of these delivered within 36 hours.—M. O. L.

The comparative physiology of the menstrual cycle. Zuckerman, S., Brit. M. J. **2**: 1093. 1932.

A philosophical dissertation based upon the author's personal observations and the related literature. He recognizes that the impossibility of conducting research into the human menstrual cycle, in the same thoroughly organized manner as has been employed in animal investigations, leaves unsettled certain points essential to a profitable comparison between human and other mammalian reproductive mechanisms. Differences between the cycle of one primate and another are conspicuous; e.g., sexual skin changes are prominent in some, inconspicuous in others, and entirely lacking in the rest. The characteristic of menstruation common to all primates is bleeding from the uterus approximately every four weeks. Citing Evans and Swezy's work he believes their deduction that "ovulation occurs at any time in the menstrual cycle" is not justified. His contention is supported by excerpts from other authors who consider that ovulation occurs about two weeks before the onset of the next menstruation. Deducing the condition of the ovaries from preconceived ideas of the corresponding picture in the uterus is dangerous for the condition of the endometrium at any moment is determined both by its own sensitivity to the hormones to which it is subjected, and by their concentration in the blood stream. Data are lacking to show that these are constant for given stages of the cycle. The point of view is adopted as most reasonable that the anterior lobe of the pituitary controls the ovarian cycle and stimulates the production of ovarian hormones. Its effect is cyclically interrupted. The ovarian secretions produce changes in the endometrium, and when their action is interrupted or decrease, subsequent to the withdrawal of the stimulus of the anterior lobe, the endometrium degenerates and menstruation ensues. The main difference between the menstrual cycle of the primates and the oestrous cycle of the lower animals lies in the distribution of their follicular phases; i.e., the period in which the follicular hormone functions. The author's separation of theory from fact is commendable; his deduction and correlation are stimulating, but explanation of menstruation—still remains in the realm of theory.—J. P. Pratt.

Anterior pituitary lobe and action of insulin (Extracto antero-hipofisario y resistencia a la insulina). di Benedetto, E., Rev. Soc. argent. de biol. **8**: 578. 1932.

Dogs treated daily with anterior pituitary extract for five days showed a fall of blood sugar when insulin was injected. The fall was equal to, or greater in extent, than in control animals, owing to the higher initial level, but the lowest figure observed was always higher. Symptoms of hypoglycemia were never present. Thyroidectomized dogs and hypophysectomized dogs behaved in a similar way. These last resisted doses of insulin that were fatal to hypophysectomized untreated dogs.—J. T. L.

Rôle of the liver in the hyperglycemic activity of the anterior pituitary lobe in toads (Papel del hígado en la acción hiperglucemiante del lóbulo glandular de la hipófisis en el sapo). Campos, C. A., J. L. Curutchet and A. Lanari, Rev. Soc. argent. de biol. **9**: 11. 1933.

Hyperglycemia produced by subcutaneous implantation of anterior pituitary lobe in hypophysectomized, pancreatectomized toads (Bufo arenarum), began 7 hours after implantation, reached its highest level in 24 to 30 hours and was over in 70 hours. In hepatectomized toads there was a gradual fall in blood sugar. Implantation of the anterior pituitary lobe prevented this fall, the blood sugar remaining at a constant level. When implantation was made 24 hours after hepatectomy and the blood sugar determined 24 hours later, the level was found to correspond to the 24th and not the 48th hour after hepatectomy. Muscle glycogen decreased in hepatectomized toads. Anterior lobe implantation partially prevented this decrease. The percentage figures were higher than in non-treated but lower than in normal animals. Hepatectomized, pancreatectomized, hypophysectomized toads had a blood sugar level slightly below normal, whether the anterior pituitary lobe had been implanted or not. Therefore the diabetogenic activity of the anterior pituitary lobe cannot take place in pancreatectomized, hypophysectomized toads in the absence of the liver.

—J. T. L.

Anterior pituitary extracts in Graves' disease (Die Wirkung den Hypophysen-Vorderlappen-Extrakte bei Hyperthyreose). Czoniczer, G. and G. Kleiner, Ztschr. f. d. ges. exper. Med. **81**: 808. 1932. Abst., Physiol. Absts. **18**: 360.

Marked diminution in the basal metabolic rate in several cases of Graves' disease was found to follow treatment with the anterior pituitary extracts, glanduantin and prähormon. Whilst the fall was not very marked in an acute experiment, continued treatment, e.g., 1 injection of 100 mouse units every 3 days for about 2 weeks, lowered the metabolic rate by as much as 50%. These results were obtained in cases which had received no benefit from the ordinary methods. The general clinical condition was also improved by the anterior pituitary injections.

The inhibition of estrus by extracts of the anterior lobe of the pituitary body. D'Amour M. C. and H. B. Van Dyke, J. Pharmacol. & Exper. Therap. **47**: 269. 1933.

The mean length of the oestrus cycle in 112 normal young mature female rats during one month was 4.39 ± 1.40. Acetone dried anterior lobe was found to be effective in inhibiting estrus and can be used as a source of the principle. Extraction at pH's above 7 gave more potent solutions than at pH's below 7. The estrus-inhibiting principle can be salted out with 20% sodium sulphate or by saturating with sodium chloride. Sheep whole pituitary was found to be uniformly more potent both in gonad-stimulating power and in its ability to inhibit estrus than was beef anterior lobe. Nine control tissues given in doses up to 40 times that of anterior lobe were ineffective in inhibiting estrus and did not produce the histologic changes characteristic of treatment with anterior lobe, i.e., absence of ripe follicles, many corpora lutea, and corpora lutea with ova enclosed. When injected daily for seven days, the mean length of the cycles increased with the size of the dosage from a minimum of 4.93 days with 3.1 mg. of dry powder to a maximum of 16.15 days with 86.8 mg.—M. C. D'Amour.

Clinical and animal experiments on the melanophoric agent of the posterior pituitary lobe (Klinische und tierexperimentelle Untersuchungen über dans Melanophorenagens des Hypophysenhinterlappens). Ehrhardt, K., Arch f. Gynäk. **148**: 265. 1932. Abst., Chem. Abst. **27**: 2191.

This agent disappears from the blood of animals 4 hours after a subcutaneous injection. It is excreted in the urine heavily for the first 24 hours and then a trace for the next 24. In pregnancy of animals and humans the melanophore hormone content of the pituitary is not increased. The melanophore reaction was positive in the 5 and 6 months old fetus.

Relationships between the anterior pituitary lobe, thyroid glands and the carbohydrate metabolism of the liver (Beziehungen zwischen Hypophysenvorderlappen, Schilddrüse und Kohlehydratstoffwechsel der Leber). Eitel, H. and A. Loeser, Klin. Wchnschr. **11**: 1669. 1932. Abst., Chem. Absts. **27**: 759.

The intraperitoneal injection of the thyreotropic substance of the anterior pituitary lobe into guinea pigs initiates morphological and functional changes in the thyroid gland resembling those of human Basedow's disease within as little as 2 hours. The liver glycogen, however, remains normal for 4 days, then begins to fall, becoming almost glycogen-free 7-11 days after the injection, due to the hyperthyroidism. The histological changes in the thyroid gradually return to normal, as does the liver glycogen in 2-3 weeks. These effects are not observed in thyroidectomized animals. A preliminary report.

Relation of thyroid activity to the pituitary gland (Schildrüsentätigkeit und Hypophysenvorderlappen). Eitel, H. and A. Loeser, Klin. Wchnschr. **11**: 1748. 1932. Abst., Physiol. Absts. **17**: 274.

In 3 human subjects daily intramuscular injection of 600 units (15 mg.) of the thyrotropic hormone of the pituitary gland for a period of 6 days gave rise to an increase of the basal metabolism. The maximum increases were 22, 43 and 39%.

Diabetogenic principle of the anterior pituitary. Evans, E. I., Proc. Soc. Exper. Biol. & Med. **30:** 1370. 1933.

A diabetic syndrome of varying intensity was produced in 12 normal dogs by alkaline extracts of the anterior pituitary. Marked lipemia, polydipsia, polyuria, and moderate glycosuria, hyperglycemia and acidosis were produced. The glucose tolerance curves changed towards the diabetic type.—M. O. L.

Present position of our knowledge of anterior pituitary function. Evans, H. M., J. A. M. A. **101:** 425. 1933. Abst., A. M. A.

In discussing the function of the substances or hormones furnished by the pituitary body the author states that sufficiently sensitive test objects have been found for each of the five substances—the growth, gonadotropic, thyrotropic, lactogenic and diabetogenic hormones—and that in many cases there are assurances of relative, even if not absolute, freedom from any but a single effect. One may also challenge the assumption that these various isolated and clear-cut effects are all the direct result each of a peculiar hormone substance acting on a particular end organ. Might not some of them be secondary, that is, indirect, effects of two or three fundamental hormones like those which govern growth and sex? The author is of the opinion that this vitally important criterion will also be met quickly. The effect of the growth hormone is, of course, general. But the effects of the gonadotropic and thyrotropic hormones have been recently shown to be exercised directly on their recipient tissues, for these secretions cause their characteristic effects when they are placed in contact with gonadal or thyroid tissue fragments in the Warburg chamber. Fortunately the biologic chemist has now joined forces with the biologist or, in the example of Collip, has taken charge of this whole affair, and one will sympathize with the impulse that leads the author to the prediction that through the use of some of the most modern tools of biologic chemistry, those for instance that have been so useful in vitamin and, above all, in enzyme research, ultimate identification of these substances will not be long delayed.

Initiation of copious milk secretion in virgin goats by anterior pituitary. Evans, E. I., Proc. Soc. Exper. Biol. & Med. **30:** 1372. 1933.

Copious lactation was induced in one dry and three virgin goats by the injection of alkaline extracts of anterior pituitary. The yield 20 days after the injection had been discontinued varied from 2 to 4 pounds. In one virgin cow a daily yield of 15 pounds of milk was secured.—M. O. L.

Sex hormones of the anterior lobe of the hypophysis; further purification of a follicular stimulating factor and the physiological effects on immature rats and rabbits. Fevold, H. L., F. L. Hisaw, A. Hellbaum and R. Hertz, Am. J. Physiol. **104:** 710. 1933.

An aqueous pyridine extract of desiccated sheep pituitary powder has been fractionated into two preparations. One fraction, which is characterized by being water soluble, is very active in stimulating growth of follicles in the ovaries of immature rats and rabbits and relatively inactive in inducing lutein development. The second fraction is more insoluble in water and is practically inactive for the stimulation of follicular growth, but is active for luteinization. It has very little action, if any, on the ovaries of immature rats but in rabbits where small follicles are already present in the ovaries it changes them to corpora lutea. If injected together with the follicular stimulating preparation it changes the developing follicles to corpora lutea in rats and rabbits. The united extracts are equivalent physiologically to the original unfractionated extract. Rats seem to be more sensitive to small amounts of the luteinizing factor than rabbits. The ovaries of rabbits are, however, readily luteinized by moderate amounts of the luteinizing hormone. Consequently the use of rabbits as test animals offers definite advantages over rats. The authors are of the opinion that the development of follicles and corpora lutea in the ovaries of rats and rabbits is due to the action of two separate principles, one which causes growth of follicles and a second which changes the follicles to corpora lutea and that these two factors have been substantially separated from one another though the separation is not entirely complete.—Authors' Summary.

The function, assay and preparation of galactin, a lactation stimulating hormone of the anterior pituitary and an investigation of the factors responsible for the control of normal lactation. Gardner, W. U. and C. W. Turner, Missouri Agriculture Exper. Station Research Bull. 196. 1933.

In this paper the authors presented further evidence on the effect and nature of a galactopoetic hormone of the anterior pituitary. They had previously verified the observations of Grüter and Stricker (1929) and Corner (1930) that the pituitary contains a lactation-stimulating hormone which they call galactin. Over 150 mature, normal or ovariectomized, female rabbits were subcutaneously injected with various fractions of pituitary extracts. Of this number over 70 responded positively. Some of the extracts were consistently found to be impotent. In other cases the lack of response was ascribed to the unfavorable developmental condition of the glands at the time of the injections. Of the 4 mature female guinea pigs treated 2 responded to galactin. Rats, mice and monkeys did not respond under the conditions of the experiments. Lactation was re-induced in a sow and a dog following the administration of galactin. The lactation-stimulating extracts were ineffective in stimulating the growth of the mammary glands of immature and young ovariectomized female rabbits and of young male rabbits. The immature glands of virgin or of male rabbits or the the involuted glands of old ovariectomized rabbits did not respond to galactin. A method of assay of galactin using the rabbit was presented. The response was quantitative in nature and was obtained most readily in rabbits with fully grown glands. Galactin was obtained from sheep and cattle pituitaries by alkaline extraction (pH 8.5) and precipitation of the active material upon neutralization and slight acidification (pHs 7.4-5.5). Its occurrence was independent of the gonad-stimulating hormone content. A continuous pseudopregnant condition maintained by periodic intravenous injections of Antuitrin-S for periods up to 35 days was not followed by lactation in mature, young, or hysterectomized rabbits. Galactin was not capable of maintaining lactation. Mammary function decreased after initiation in the presence of continuous injections. Following a galactin-induced lactation the glands remained unaffected by further treatment for a period of at least two weeks.—W. U. Gardner.

Anterior pituitary extract and plasma proteins (Extracto ántero-hipofisario y proteínas del plasma). Goldberg, I., Rev. Soc. argent. de biol. **8**: 610. 1932.

Normal (8) and thyroidectomized (2) dogs were injected intraperitoneally with 5-7 daily doses of 7 cc. per kg. anterior pituitary lobe extract (Evans and Simpson's 1 cc.=0.2 g. fresh gland). Total plasma proteins increased on average 12.9% (maximum 31.2%). Albumin increased more (14.1%) than globulins (10.9%). The albumin-globulin ratio showed only slight variations. Nonprotein N increased in 5 of 7 cases observed. Viscosity increased on average 20% (maximum 51.2%). The same changes were produced by anterior pituitary treatment in the recently thyroidectomized dogs, but the increase in globulins was more pronounced and the albumin-globulin ratio diminished.—J. T. L.

Effect of luteinizing and follicular stimulating fractions of pituitary on the thyroid. Greep, R., Proc. Soc. Exper. Biol. & Med. **30**: 1362. 1933.

The effects of follicle-stimulating and luteinizing extracts of anterior pituitary on the thyroid glands of 14 young guinea pigs were compared. The follicular stimulating fraction produced no significant histological or weight changes. The luteinizing fraction caused 50 to 145% increase in thyroid weight and histological changes indicating intense secretory activity. Castration did not alter the response.—M. O. L.

Cellular constituents of the anterior hypophysis after uterine implants of carcinoma in rats. Guyer, M. F. and P. E. Claus. Anat. Rec. **56**: No. 4. 1933.

In an earlier histological study of the anterior hypophysis of 32 rats (22 experimental animals and 10 controls) it was found that a marked increase in the number of basophile cells occurred after subcutaneous implants of "Flexner-Jobling carcinoma," with no perceptible change in the oxyphile cells. The histological picture was essentially that which follows castration. Likewise, increased ovarian size and sexual precocity were induced in 12 immature mice by transplants of such hypophysial material from 39 cancerous rats. Uterine transplants of this same carcinoma, according to estimates based on 100 counts

from 8 rats with well-developed uterine cancer, were followed by marked increase in the number of oxyphile cells and but slight increase in the number of basophile cells. The histological picture is the same as that which is associated with pregnancy or with injections of oestrin. The oestrual cycle continues, however, and sections of the ovaries disclose the usual histological picture of the non-pregnant rat. Daily injections of 4 rat units of water-soluble oestrin (theelin) did not prevent the formation of castration cells in the anterior hypophysis of either 10 castrated animals or of 5 with subcutaneous cancer studied histologically from this standpoint, although such treatment kept the females in a state of almost continuous oestrum.—M. F. Guyer.

The influence of the hormone of the anterior lobe of the pituitary present in pregnancy urine on the ovaries of adult mice (Über die Einwirkung der im Schwangerenharn vorhandenen Hypophysenvorderlappenhormone). Hirsch-Hoffmann, H. U., Zentralbl. f. Gynäk. **56**: 2538. 1932.

In 104 of 111 adult female mice characteristic Aschheim-Zondek reactions were observed 36 hours after injection of 3.6 cc. of urine of pregnant women. Similar changes were noticed in 14 pregnant mice treated in the same manner. These changes were not observed in uninjected adult mice, or in mice receiving urine from non-pregnant women. Eighty-two animals were used. The author believes it possible to diagnose pregnancy by using the adult as well as the immature mouse as test animal in the Aschheim-Zondek test.—O. S. Baum.

Asthenia of hypophysectomized toads (La astenia de los sapos hipofisoprivos). Houssay, B. A., Rev. Soc. argent. de biol. **9**: 34. 1933.

Hypophysectomy or extirpation of the anterior pituitary lobe was followed in B. arenarum by a neuro-muscular syndrome beginning with a disturbance of the postural reflexes. Afterwards there was hypotonia, adynamia, increasingly slower movements and general muscular weakness; sometimes convulsions occurred. These symptoms were not related to the formation of the brown pellicle. The pellicle is usually shed when asthenia is most pronounced; it is also produced after cauterization of the tuber cinereum without the occurrence of asthenia. The injection of glucose, adrenaline and Swingle and Pfiffner's cortico-adrenal extract did not modify the nervous symptoms following hypophysectomy; their appearance may be prevented by administration of anterior or posterior pituitary lobe extract implantation. Injection of anterior or posterior pituitary lobe extracts does not modify the course of adrenal insufficiency in adrenalectomized toads.—J. T. L.

Action of anterior pituitary extract on blood iodine of thyroidectomized and hypophysectomized dogs (Hipófisis y Tiroides. XVI. Acción del extracto ánterohipofisario sobre la iodemia de los tiroprivos y de los hipofisoprivos). Houssay, B. A., A. Biasotti and P. Mazzocco, Rev. Soc. argent. de biol. **8**: 554. 1932.

Intraperitoneal injection of the anterior pituitary extract (Evans and Simpson's) in 6 daily doses of 10 cc. (1 cc.=0.2 g. fresh gland) produced an increase in blood iodine in normal and hypophysectomized dogs. It produced a decrease in thyroidectomized dogs. It is believed that the anterior pituitary has a double regulatory activity on the blood iodine. By means of its excito-thyroid function it increases and by an extra-thyroid activity it reduces blood iodine.
—J. T. L.

Diabetogenic activity of anterior pituitary extracts (Acción diabetógena de los extractos antero-hipofisarios [3°nota]). Houssay, B. A., A. Biasotti, E. di Benedetto and C. Rietti, Rev. Soc. argent. de biol. **8**: 563. 1932.

Extracts were prepared by Evans and Simpson's technique; intraperitoneal injections were made for 5 to 7 or more days in doses of 7 cc. per kg. (1 cc.=0.2 gm. fresh gland). In 15 normal fed dogs glycemia increased, the average blood sugar being 177 mg. per cent after treatment. In 19 dogs injected with extracts of thyroid, muscle and kidney no increase was seen; when posterior pituitary extract and adrenaline were given blood sugar was normal or only slightly increased 18 hours later. Hypophysectomy and thyroidectomy did not alter the hyperglycemic effect of anterior lobe extract. Diuresis was considerably increased (50 to 500%) by the extract, not by extracts of other tissues. Glycosuria was observed when the blood sugar rose above 175 mg. per cent; 0.75 to

2.3 gm. sugar per day were excreted by the kidney. Other extracts did not produce glycosuria; 0.5 mg. per kg. adrenaline gave a slight glycosuria, 0.25 mg. per kg. daily during 4 days produced no glycosuria. There was not a significant rise in urinary N. Ketonic bodies appeared in the urine, their excretion being in relation with the degree of glycosuria and hyperglycemia; other extracts did not produce ketonuria. Body weight varied slightly. Fasting dogs (4 animals) had no hyperglycemia, glycosuria or ketonuria after 5-6 days' treatment with anterior lobe extract.—J. T. L.

Anterior pituitary extract in phlorizin diabetes (Acción del extracto anterohipofisario sobre la diabetes floridínica). Houssay, B. A., A. Biasotti, E. di Benedetto and C. T. Rietti, Rev. Soc. argent. de biol. **8**: 570. 1932.

Three normal and 3 hypophysectomized dogs were treated with Evans and Simpson's extract, 2 controls with kidney extract and 2 with muscle extract. They were fed 250 gm. meat daily during 6 days, then all food was suppressed; on the eighth day and for the following 5-6 days 1 gm. phlorizin in 10 cc. olive oil was injected subcutaneously. During the whole period they received 7 cc. per kg. of the extract (1 cc.=0.2 gm. fresh gland). The blood sugar gradually rose to 236, 255 and 175 mg. per cent in the 3 normal dogs treated with pituitary extract during the period of meat diet; it rose to 181-132 mg. per cent during the meat diet period in the hypophysectomized. During the 2 days' fast the blood sugar returned to high normal values. Hypophysectomized dogs not treated with extract, when injected with phlorizin and kept fasting have hypoglycemia and die. Extracts of muscle and kidney did not increase glycemia during the meat diet and during phlorizin treatment a marked decrease in glycemia was observed in these dogs. Glycosuria during phlorizin injections was less marked in normal dogs treated with extract than in the controls; 1.53 gm. and 2 gm. per kg. per day were the respective averages. Hypophysectomized dogs eliminated more sugar during the phlorizin period when treated with extract than when not so treated (1.74 g. and 0.68 g. per kg. per day, respectively). Diuresis was increased during the phlorizin period in all the animals, hypophysectomized not treated animals had little or no increase in diuresis when phlorizin was injected. Ketone bodies in the urine of hypophysectomized phlorizinized dogs increased in those treated up to the level found in normal controls. Urinary nitrogen did not increase significantly. The D:N ratio was so high that all sugar eliminated could not have come from proteins. Loss of weight was more marked in the hypophysectomized phlorinized dogs when treated with extract than in controls not treated. These observations show that when anterior pituitary extract replaces the hormone absent in hypophysectomized dogs, phlorizin diabetes had the same course in treated dogs as in the controls.—J. T. L.

Hypophysis and thyroid; action of extirpation and implantation of the hypophysis on the thyroid of B. arenarum (Hipófisis y tiroides. XV. Influencia de la ablación o implantatión de la hipofisis sobre la tiroides del sapo). Magdalena, A., Rev. Soc. argent. de biol. **8**: 542. 1932.

Hypophysectomy in toads produces thyroid atrophy; the height of the epithelium is reduced to one-half that found in normal controls. Simple craneotomy and cauterization of the tuber cinereum do not produce thyroid atrophy. Implantation of the anterior pituitary lobe increases the height of the epithelium to almost twice the normal size; the colloid is reduced; the circulation increased. A definite reaction, but of lesser degree, is obtained by the implantation of anterior lobe of rats, steers, hen and a fish (Pseudoplatystoma coruscans Ag). No increase was observed after implantation of posterior pituitary lobe, testicle, kidney, ovary, liver, spleen, muscle and tuber cinereum. The effect is therefore specific for the anterior lobe.—J. T. L.

The effects of the gonadal-stimulating hormone of the anterior pituitary on the voluntary activity, the age of maturity and the size of the litter in immature female albino rats. Kraft, Ruth M., Am. J. Physiol. **102**: 355. 1932.

Anterior-pituitary tissue and extracts of the gland were injected into sexually immature female albino rats, which were the progeny of either normally matured or precocious sexually matured mothers. In all 330 controls and 730 experimental animals were studied. Treatment was begun at the age of 18 to 22 days. The total voluntary activity was not significantly changed except in

the group treated with an extract—that had been filtered through a porcelain filter—in which case there was a marked decrease. The voluntary activity (as shown by the revolving cage method) showed no cyclic variations similar to those of normal sexually matured females. Vaginal smears failed to show the typical oestrual cycle, which may have been due to luteinization of the ovary or to a marked shortening of the cycle. Precocious sexual maturity was produced in from 17 hours to three days following treatment. This was evidenced by the canalization of the vagina and by conception and the bearing of young. In one case young were produced when the mother was only 48 days old. The litters of these animals were much larger than their controls and their sex ratio was significantly lower. All of the effects noted were more pronounced in the second generation of experimental animals which may mean that at least a part of the effect is transmitted to the young.—Author's Abst.

The effect of extracts of the anterior pituitary lobe on growth (Experimentelle Untersuchungen zur Frage der Wachstumswirkung von Hypophysenvorderlappenextrakten). Lucke, H. and R. Hückel, Arch. f. exper. Path. u. Parmakol. **169**: 290. 1933. Abst., Chem. Abst. **27**: 2189.

Daily intramuscular injections of an anterior pituitary extract into white mice over a period of more than 6 months accelerated growth, without affecting the definitive weight finally attained. In some cases there was histological evidence of cartilaginous hyperplasia and degeneration in the upper tibial epiphysis, resembling the early arthritis seen in human acromegaly.

Anterior pituitary extract and blood glutathione (Influencia del extracto ánterohipofisario sobre el glutation saguíneo). Maveroff, H., Rev. Soc. argent. de biol. **8**: 614. 1932.

Normal (6), hypophysectomized (2) and thyroidectomized (2) dogs received intraperitoneally 5 daily doses of 7 cc. per kg. anterior pituitary lobe extract. Blood glutathione was determined by Marenzi and Braier's method. In the cells it increased constantly in all the animals; in total blood it varied erratically owing to the frequent decrease in cell volume observed.—J. T. L.

Specific dynamic action in fasting hypophysectomized dogs after lesion of tuber cinereum (Ayuno y acción específica dinámica en perros hipofisoprivos y con lesión tuberiana). Mazzocco, P., Rev. Soc. argent. de biol. **8**: 621. 1932.

Hypophysectomized dogs (9) had a lower basal metabolism (745 cal. per sq. m. over 24 hours) than those (5) with lesions in the tuber cinereum (796 cal.) and normal ones (9 dogs, 888 cal.). After ingestion of meat the rise in respiratory metabolism was similar in hypophysectomized and normal dogs, those with tuber lesions had a more marked rise. After 76 hours' fasting a slightly more pronounced specific dynamic action was seen. In the dog the pituitary is not a necessary factor in specific dynamic action.—J. T. L.

Anterior pituitary lobe extract and blood lipids (Acción del extracto de lóbulo anterior de hipófisis sobre la grasa sanguínea). Muñoz, J. M., Rev. Soc. argent. de biol. **8**: 587. 1932.

Four normal dogs received 7 cc. anterior pituitary lobe extract (Evans and Simpson's) for 5 days (1 cc.=0.2 gm. fresh gland). They were fed 200 gm. meat daily. After a 48-hour fast (24 hours after the last injection) blood samples were drawn. A marked increase in total fatty acids, cholesterol and phospholipids was seen. Hypophysectomy produces a slight decrease in the concentration in blood of these same substances.—J. T. L.

Posterior pituitary lobe and imbibition in batrachians (Lóbulo posterior de la hipófisis e imbibición de los batracios). Novelli, A., Rev. Soc. argent. de biol. **8**: 631. 1932.

Injections of posterior pituitary lobe extract produce an increase in weight in Bufo arenarum and Leptodactylus ocellatus, proportional to the dose injected. The maximum effect is seen in 8-10 hours, after that it decreases slightly. L. ocellatus is more sensitive than B. arenarum; the greatest increase in weight was obtained with 5 mg., being 24.4% and 17.7%, respectively. Pitressin and Pitocin are both active, but the latter only about one-third as much as the first.
—J. T. L.

Pituitary hormones and the male genital organs (Ormone preipofisario ed apparato genitale maschile; Contributo al problema della maturazione puberale). Pighini, G., Biochem. e. terap. sper. **20**: 161. 1933.

Human hypophysis extract produced in young male rats a precocious differentiation of puberty of the gonads and a considerable hypertrophy of the other part of the genital tract: vas deferens, seminal vesicles, prostate, penis. Large doses produced degeneration of the seminal canals and hypertrophy of the interstitial parts. Puberty is developed in the male less rapidly than in the female: this depends probably on the higher bodily and psychic differentiation of the male in that period of development.—A. E. Meyer.

The energy basis of endocrine action (hypophysis); the metabolism of the testicle under the influence of the sexual hormone of the anterior lobe of the hypophysis (Über energetische Grundlagen endokriner Wirkungen. II. Die Stoffwechselreaktion des Hodens unter dem Einflusse des Hypophysenvorderlappensexualhormons). Reiss, M., H. Druckrey and F. Fischl, Endokrinologie, **10**: 329. 1932.

The hormone used was prepared from pregnancy urine by the method of Biedl. The metabolism of the testicles in horse serum was measured by the method of Warburg and lactic acid analysis performed by Mendel-Goldscheiderschen's method. By the injection of this hormone into immature rats the weight of the testicles increased very markedly, the CO_2 output and O_2 consumption increased and the lactic acid content increased from 60.7 mgm. per cent to as high as 299 mgm. per cent. With adult rats there were no significant changes in either O_2 consumption, CO_2 output or in the lactic acid content of the testicles. The authors believe the increased growth is due to the ability of this hormone to bring about glycolysis under aerobic conditions.—E. L.

The rôle of growth hormone in the metabolism of liver and kidney (Über energetische Grundlagen endokriner Wirkungen; Die Rolle des Wachstumshormons im Stoffwechsel von Leber und Niere). Reiss, M., A. Hochwald and H. Druckrey, Endokrinologie, **13**: 1. 1933.

The relation of pituitary growth hormone to gaseous metabolism in the liver and kidney and to glycogen transformation in the liver was studied in rats. Extracts were made by the Van Dyke and Wallen-Lawrence method as well as by a method of acetone-alkaline extraction personally devised that gave an extract free of thyrotropic and luteinizing fractions. The tissues were studied by the Warburg method. In 5 controls the O_2 consumption in the kidney ranged from 19.0 to 21.2 and the CO_2 output from 11.8 to 16.7. In the liver the respective ranges were 9.2-11.6 and 5.5-6.3. In 12 hypophysectomized animals the oxygen consumption in the kidneys ranges definitely lower—from 11.1 to 15.8; similarly in the liver the range was from 1.8 to 3.9. The CO_2 was likewise depressed. Comparable results were obtained in the liver. Nine animals from which the pituitaries were incompletely removed gave intermediate findings. Nine animals were treated with growth hormone. The oxygen consumption in their kidneys (8 cases tested) was increased above the normal, the range being now from 13.5 to 27.8, but 6 of the 8 transcending 20. Comparable results were obtained in case of the CO_2 output as well as in case of both gases in the liver. It appeared that the growth hormone increased the anaeropic glycolysis and caused the appearance in the liver of aerobic glycolysis as well.
—R. G. H.

Differentiating some functions of the anterior pituitary hormones. Riddle, Oscar, Ann. Int. Med. **7**: 23. 1933.

Present possibilities of identifying specific responses with specific pituitary hormones are considered. Tabulated data for ring doves indicate that neither gonad-stimulating hormone, prolactin, nor prolan alone increases liver size; probably all preparations rich in both growth and gonad-stimulating principles do markedly enlarge the liver. These data indicate that liver enlargement following the administration of extracts of the anterior pituitary, like a similarly induced glycosuria, is probably a non-specific, secondary and pathological response—reflecting a functional dysharmony incident to the simultaneous presence in the blood of large amounts of two or more potent principles which never normally thus coexist in the blood.—Author's Abst.

Increased skeletal effects in anterior pituitary growth-hormone injections by administration of thyroid in hypophysectomized, thyro-parathyroidectomized rats. Smith, P. E., Proc. Soc. Exper. Biol. & Med. **30**: 1252. 1933.

Growth hormone, with and without concurrent thyroid feeding, was administered to rats from which both the pituitary and thyroid glands had been removed. In every case the skeletal growth and in some animals the weight increase was greater in the rats receiving both thyroid and growth hormone than in their litter mates receiving growth hormone alone.—M. O. L.

Effect of injecting pregnancy-urine extracts in hypophysectomized rats; the male. Effect of injecting pregnancy-urine extracts in hypophysectomized rats; the female. Mating reaction of hypophysectomized male rats treated with pregnancy urine extracts. Smith, P. E. and S. L. Leonard, Proc. Soc. Exper. Biol. & Med. **30**: 1246; 1248; 1250. 1933.

In male hypophysectomized rats the injection of anterior pituitary-like substance from pregnancy urine prevented the testicular atrophy and even caused enlargement in some. There was a pronounced stimulation of the seminiferous tubules. The injection of the material into 40 female hypophysectomized rats invariably caused enlargement of the ovaries, marked interstitial cell hypertrophy and formation of new corpora lutea. The vaginal smear showed a constant cornified type. Eleven of 25 mating attempts with 6 hypophysectomized males, treated as above, were fertile and normal litters were produced.
—M. O. L.

Implantations of anterior pituitary glands in alopecia. Stanley, L. L. and J. O. Hawkins, M. J. & Rec. **137**: 462. 1933.

There were 14 cases treated in this series. In all, 40 implantations were performed. Two of the patients took by mouth one-half of a gland preserved in alcohol each day for two months. Four of the implantations, or 10%, became infected and sloughed out. Of the patients treated, one had been a drug addict, two had had typhoid fever, two had had tuberculosis, and two had had syphilis. Four, or 29%, showed a marked growth of hair. Three showed a slight growth. Seven demonstrated no change in the hair of the head. Seven reported that the scalp had become more oily. Six showed that dandruff had entirely disappeared. Two showed that there was more sweating of the scalp. Two noticed an increase in the growth of body hair. As to constitutional effects, one said that chronic indigestion and constipation from which he had suffered for years, had completely disappeared. Another reported that he had become more nervous since receiving the gland implantation. This study extended over a period of seven months.—Authors' Summary.

Effect of growth-promoting extracts of bovine anterior hypophysis on hypophyses of castrated albino rats. Targow, A. M., Proc. Soc. Exper. Biol. & Med. **30**: 1126. 1933.

It is concluded that growth-promoting extracts of the anterior pituitary when injected for approximately 6 weeks following castration do not prevent the increase of gonad-stimulating potency of the hypophysis, as revealed by the implantation technique, yet do cause a marked diminution in weight of both the anterior and posterior lobes. The data from 120 animals were analyzed statistically by the method of paired comparisons.—M. O. L.

Cause of hyperkeratosis produced in toads by hypophysectomy and lesion of the tuber cinereum (La causa de la producción de una película cutánea en el sapo hipofisoprivo o con lesión tuberiana). Ungar, I., Rev. Soc. argent. de biol. **8**: 616. 1932.

Daily injections of anterior pituitary lobe extract (Evans and Simpson's) or implantation of anterior pituitary lobe prevent the formation of a pellicle on the skin of toads (Bufo arenarum) after the anterior lobe has been extirpated. Non-treated controls showed marked keratosis. Once the pellicle had been formed it was shed after a few days' treatment with extract. Extracts of testicle, liver, muscle, posterior pituitary lobe and adrenal gland did not have this effect. Brain extract was toxic, the animals died after 5 days' treatment, the pellicle being shed shortly before death. Thyroxine (0.3 mg. daily) had a rapid curative action, the pellicle was shed in 2 days. Thyroidectomy does not

produce keratosis. Anterior lobe extract as well as thyroxine were active in thyroidectomized, hypophysectomized toads.—J. T. L.

Chemical findings in psychiatric patients; relations to the hormonal system (Chemische Befunde bei psychisch Erkrankten. Beziehungen zum hormonalen System). Zondek, H., München. med. Wchnschr. **79**: 614. 1932.

Report of a lecture. The number of subjects and technique of tests were not stated. The bromine concentration in the blood is 1:1/100. The bromine picture is extremely constant. Only in manic depressive psychoses is it about 40-60% under the normal in the endogenous but not in the reactive types. The anterior lobe of the pituitary contains exceptionally high amounts of bromine. In prolonged somnifen narcosis of dogs occurs increase of the bromine content of the medulla oblongata drawn from the pituitary. A thyroxine-derivative in which iodine was substituted by bromine produced highly pronounced weariness. —G. L. Banay.

The treatment of hypophyseal cerebral emaciation with hormone of the anterior lobe of the pituitary, Prolan (Behandlung der hypophysärzerebralen Magersucht mit dem Hypophysenvorderlappenhormon Prolan). Zondek, H. and Gertrude Koehler, Med. Klin. **28**: 1125. 1932.

The authors present four cases of unexplained emaciation, one male aged 18 and three females aged 17, 15 and 35 years. All showed low basal metabolic rates (about —30%) and all presented a low specific dynamic action. Zondek, following Kestner, places some emphasis upon this latter finding in pituitary disease. None of the patients was helped by routine treatment or the use of insulin, arsenic or calcium. All were greatly improved by the use of prolan, 100 rat units intramuscularly each day and 150-200 rat units by mouth for a period of many months. Zondek advises treating early mild cases as the well advanced cases do not respond. No report is given of metabolic rate determinations after "cure." Although the exact clinical diagnosis can hardly be accepted without doubt in these cases, there is no reason for not attempting glandular therapy with pituitary hormone (anterior lobe) in unexplained cachexias.—S. Silver.

The use of insulin in the treatment of menorrhagias of ovarian etiology and in particular in hemorrhagic metropathy (Do valor da insulina no tratamento das metrorrhagias de causa ovariana, e em particular da metropathia hemorrhagica [com dez observaçoes]). Azevedo, G. V., Rev. de gynec. e d'obst. **26**: 358. 1932. Am. J. Obst. & Gynec. **26**: 143.

The author discusses those cases of uterine bleeding in which a microscopic examination of the endometrium demonstrates a glandular hyperplasia, distinctly different from the menstrual mucosa. This peculiar hyperplasia is due to the disturbed ovarian function, and responds to insulin therapy. Several investigators have found that there is a definite relationship between the pancreas and the ovary. Insulin is also indicated in the menorrhagias occurring during the course of acute and chronic inflammations of the adnexa. The dose of insulin is usually 20 to 40 units per day. In some cases the dose must be increased, preferably administered in divided doses throughout the day. Several cases are reported which responded to insulin therapy when all other methods of treatment had failed.

The treatment of diabetes. Blotner, H., M. Clin. North America, **16**: 907. 1933.

The author presents two patients with diabetes, one having been treated with insulin and the other without. Both were treated as out-patients and neither lost any time because of the treatment. The first patient, who was more than 50 pounds underweight, was taught to keep a record of her urine with Benedict's solution, to inject herself with insulin, and to follow a simplified but interesting and palatable diet. Under this regime she gained 27 pounds in one year, is very much stronger, needs less insulin, takes an increased diet, and rarely shows glucosuria. The second patient, who was 16 pounds overweight, was given a low calory diet and taught to test and keep a record of her urine. In seven years of observation, her weight has been slowly reduced by 20 pounds and her diet gradually increased. She has been sugar-free except after overeating, and self-discipline corrects this condition. Diabetic therapy now can be

made very simple. Hospitalization of all patients is by no means essential and elaborate laboratory equipment is usually unnecessary for good results, provided the patients are coöperative and show reasonable intelligence in carrying out their instructions.—I. B.

Insulin neuritis; a case report. Caravati, C. M., Virginia M. Monthly, **59**: 745. 1933.

By insulin neuritis, Caravati refers to subjective symptoms usually in the lower extremities, such as pains, numbness, tingling and thermal changes, which the patient complains of at a rather short interval after the beginning of daily injections of insulin. At times, though rarely, these discomforts are marked and continue as long as insulin is administered. When insulin is discontinued these parasthesias usually disappear in three or four days, only to be manifest again after the resumption of insulin therapy. Neuritis associated with diabetes is a common ailment and disturbances along the peripheral nerves usually are improved or disappear when the patient is sugar-free, but no reference of a neuritis caused by insulin can be found in the available literature. The author reports a case of insulin neuritis that was relieved by a change of the brand of the product. Insulin was discontinued in this case for a short time and the symptoms of neuritis which had developed subsequent to insulin therapy almost immediately subsided. A change to the first brand was tried at intervals and each time the neuritis recurred. The author feels justified in concluding that idiosyncrasy to certain forms of insulin is responsible for the symptoms in this case.—Author's Abst.

The absorption of insulin from the gastro-intestinal tract; the effect of calcium lactate, sodium bicarbonate and blood serum in depancreatized dogs. Eaton, A. G. and J. R. Murlin, Am. J. Physiol. **104**: 636. 1933.

Insulin, given by stomach tube, along with calcium lactate and sodium bicarbonate, to depancreatized dogs (number not stated) caused a lowering of blood sugar, decrease or disappearance of sugar from the urine and a rise in R.Q. The dosage used was large (ca. 200-400 units) and only a small part of the insulin was absorbed. The results were consistent. Some of the experiments showed a higher kidney threshold for sugar, but this was probably not an effect of the treatment. Blood serum added to the above mixture brought about increased insulin absorption. The mechanism is not yet clear.—R. G. H.

Parotid hypertrophy a sign of diabetes mellitus (Paratishypertrophie, ein Symptom des Diabetes Mellitus). Flaum, E., Klin. Wchnschr. **11**: 1704. 1932. Abst., Physiol. Absts. **17**: 266.

Attention is drawn to the frequency of enlargement of the parotid gland in diabetics. Of 27 cases of parotid swelling investigated, 16 had a more or less marked glycosuria on an ordinary diet. The 11 cases without glycosuria when submitted to a sugar tolerance test showed a failing sugar tolerance.

Insulin and thermoregulation (Insulin und Wärmeregulation). Geiger, E., Arch. f. d. ges. Physiol. **229**: 578. 1932.

The experiments were performed on dogs which had fasted for 12-24 hours. Under local anesthesia, a cannula was placed in the jugular vein. The animals were then anesthetized by injecting 0.09 gm. of chloralose per kilogram through the cannula. The carotids were carefully freed from the vagi. The animals were placed on a warm table so that cooling would be prevented. The blood sugar, body temperature (rectal) and head temperature (under the tongue) were usually taken at intervals of 30-60 minutes. Under normal conditions the blood sugar and temperatures remained remarkably constant. When the carotids were warmed by the method of Kahn, the blood sugars which had varied from 72-94 mgm. in a series of 6 dogs fell in two hours to amounts varying from 39-63 mgm. per 100 cc. of blood. There was also a rise in the temperature of the head, the highest being 39.2 degrees C. After the vagi were cut below the diaphragm there was no hypoglycemia produced by warming the carotids. By cooling the carotids with the vagi intact hyperglycemia was produced. From these results the author feels that warming of the central nervous system produces a hypoglycemia due to increased activity of the vagus causing an increased output of insulin from the pancreas.—E. L.

High carbohydrate and high fat diets. Greisheimer, Esther M., Edith Goldsworthy and Gertrude Thomas, Proc. Soc. Exper. Biol. & Med. **30:** 1426. 1933.

The glucose tolerance in a normal subject was not significantly altered by a very high carbohydrate intake, over a period of 7 days. After 7 days on a high fat diet the response to the glucose tolerance test was typical of diabetes mellitus; the tolerance rapidly returned to the usual type, after return to the balanced diet. Since the diet can so markedly influence the tolerance, this should be kept in mind in glucose tolerance studies. The urea nitrogen and total non-protein nitrogen vary markedly with different dietary conditions. The fasting blood sugar is markedly influenced by a diet low in carbohydrate. A high intake of carbohydrate seemed without effect on the fasting blood sugar. —M. O. L.

Diabetic coma. Joslin, E. P., H. F. Root, P. White, A. Marble and H. M. Hunt, M. Clin. North America, **16:** 793. 1933.

The records of 221 cases of coma occurring in 189 diabetics with 29 deaths are analyzed. Since discharge from the hospital during the past nine years, 18 more cases have died. Two cases are untraced, 140 cases have been traced to Oct. 1, 1932. The mortality of the present series of 42 cases is 5%, and of the entire series of 221 cases 13.1%. Sixty-three per cent of the cases were females. In August, September and October, 1932, 86 of the 221 cases of coma occurred. Insulin dosage during the first 24 hours was 201 units as compared with 252 units in the previous 74 cases. Three cases received 510 to 520 units and all recovered. The mortality in coma increased from nil (11 cases) in the first decade, 8 and 9% in the third and fourth decades, and reached a maximum of 33% for three cases in the eighth decade. The chief cause of death in the hospital for 29 cases was sepsis and metastatic infection, and the most frequent cause of death after discharge from the hospital was pulmonary tuberculosis. Twenty-two per cent of the cases occurred in the first year of diabetes. Eighty-eight of 89 children with onset of diabetes before the fifteenth year recovered from coma. In 14 cases the plasma cholesterol was studied and found within normal limits in three cases. A low cholesterol value in coma is highly important, suggesting a mild type of coma in which insulin must be used conservatively to avoid hypoglycemia, or possible complications such as pulmonary tuberculosis, hyperthyroidism, severe pernicious anemia, or severe inanition. Complications with pregnancy and appendicitis are reported. At discharge from the hospital in 1932, the diets contained an average of carbohydrate, 133 gm.; protein, 68 gm., and fat, 83 gm. The authors feel that there should be far greater endeavor to prevent diabetic coma in the community. We should more actively follow up our diabetic patients after discharge and insist that they keep in touch with their family physicians.—I. B.

Insulin therapy in certain disorders of nutrition. Lueders, C. W., M. J. & Rec. **138:** 119. 1933.

The injection of insulin once or twice daily to the average total amount of 40 units daily produced in a selected group of 35 patients suffering from certain disorders of nutrition, with but few exceptions, a striking gain in weight, strength, physical and nervous well-being. A restoration to normal of motor and secretory function of the digestive tract was especially noted and maintained after the cessation of insulin. The weight records showed that the gain in weight, whether small or great, in the majority of patients, was either maintained or moderately increased over the course of a year, in some patients for almost two years. Routine blood sugar tolerance tests are absolutely essential before instituting insulin therapy. However, hypoglycemia may be present when the glycogen storage is exhausted and glucose assimilation lost. In such cases glucose intravenously is combined with the insulin treatment. Ten patients of the group exhibited a markedly poor tolerance for glucose. On first thought one is led to classify these cases as either "functional" or true diabetes. However, it is most difficult to differentiate hyperglycemia due to decreased glycolysis of pancreatic insufficiency from hyperglycemia due to a deranged power of glycogen storage or hepatic insufficiency. The newer functional liver tests may help solve this problem. Two of the three patients with pernicious anemia have had no relapse in 18 months, following insulin therapy and without liver therapy. The primary anemia in the two patients may possibly be due either to pancreatic insufficiency or to the loss of the essential factor temporarily restored by the stimulatory activity of insulin. Undernutrition from any cause, with the

exceptions noted above, should have the benefit of insulin therapy, even though a course of treatment must be occasionally repeated to maintain the weight and strength. Its action is at times dramatic in the restoration to normal of digestion, assimilation and bodily nutrition.—Author's Summary.

The control of carbohydrate metabolism. Macleod, J. J. R., Lancet, **1**: 1079. 1932. Abst., Chem. Absts. **27**: 2196.

Searches for the exact nerve center responsible for hyperglycemia are described. Such a center, if it exists, would have to be within the pons or the adjacent regions of the cerebellum. The rate of sugar production is regulated by alterations in the balance between insulin and adrenaline in the blood, but when there is a sudden call for sugar to meet the demands of great muscular activity direct nervous stimulation of sugar secretion by the liver is set up. It is possible that the sugar concentration of the blood supplying the nerves is the stimulus which regulates this balance.

Hypertension, obesity and hyperglycemia. Musser, J. H. and D. O. Wright, J. A. M. A. **101**: 420. 1933. Abst., A. M. A.

The authors present the average figures obtained from a group of 30 fat women who had an elevated blood pressure and hyperglycemia This was done to determine whether their obesity was associated with the inability properly to utilize carbohydrate and to see whether there was any definite relationship between the hypertension and the sugar curve. It was found that all these patients exhibited a lowered tolerance to sugar. It would seem that there is a definite syndrome in which obesity, hypertension and hyperglycemia are associated, probably with ultimate arteriosclerosis. However, in respect to the latter, in no one of the authors' patients was arteriosclerosis clinically demonstrable. Many of the patients may have had arteriosclerosis due to the fact that their age was ten years greater than the control groups. It is rather difficult to conceive of pressures as high as some of the systolic and diastolic pressures in these women existing without a concomitant peripheral sclerosis. The authors cannot make a definite statement about the relation of the diminished sugar tolerance to hypertension either from the data of their studies or from a review of the work of others. The relationship of obesity to hyperglycemia is that the obese individual is much more likely to develop diabetes than is the thin person. It seems reasonable to assume that there is no one factor definitely responsible for the combination of obesity, hypertension and hyperglycemia unless it is obesity. The reduction in weight is often associated with a lowering of the blood pressure and a return of a sugar tolerance curve to normal.

Again on the hypoglycaemic ability of insulin upon rabbits doubly suprarenalectomized or splanchnicotomized. Ohmi, F., Tohoku J. Exper. Med. **21**: 211. 1933.

Insulin was injected subcutaneously in a dose of 0.5 unit per kilo of body weight into rabbits (5 normal, 7 bilaterally suprarenalectomized, 6 with one adrenal removed and the other demedullated and 4 splanchnicotomized). While normal rabbits showed almost no convulsive attacks, these occurred in half of each set in other kinds of animals. The intensity of hypoglycaemia was not only on an average undoubtedly, though not excessively, larger in the operated compared with the normal control animals, but also a similar tendency was noticeable when the cases without convulsions only were compared. The bottom of the hypoglycaemia stage was reached definitely earlier in the experimental than in the control subjects.—R. G. H.

New cases of combined pernicious anemia and diabetes. Root, H. F., New England J. Med. **208**: 819. 1933.

Thirty-one cases of combined pernicious anemia and diabetes are analyzed in addition to the 48 previously reported. Diabetes apparently developed before the anemia in 24 of the cases. It appears that the occurrence of anemia in diabetic patients is fairly frequent, especially during complications such as pyogenic infections. The disorder may remain of uncertain type for a considerable period before developing the characteristic features of pernicious anemia.

—J. C. D.

Treatment of the same diabetic patient with widely varying diets. Strouse, S. and S. Soskin, Tr. A. Am. Physicians, **47**: 317. 1932.

The authors found that under controlled conditions the diabetic manifestations of their patients could be kept in hand by almost any dietary system. Impartial observation of the tendencies of the various special diets lead to the conclusion that the good results obtained by widely divergent dietary schemes may be due to a common denominator such as a comparatively low calorie intake possessed by most of these schemes. In a series of cases the authors administered in the same patient successively isocaloric diets varying widely in their protein, fat, and carbohydrate contents. Each patient was treated with three successive isocaloric diets, i.e., relatively high in carbohydrate, relatively high in fat, and relatively high in protein, respectively. During each period sufficient insulin was given to control the diabetic manifestations to about the same degree but the authors purposely did not attempt to render the urine entirely sugar free. The diets varied widely in composition—more widely than would be the case in therapeutic diets encountered at different clinics, but not as widely as possible, in order to avoid untoward subjective reactions in the patients. The order in which the diets were given varied in the different patients. Diabetic manifestations of all patients were adequately controlled on the various diets, and there is nothing to indicate that each of these diets could not have been continued indefinitely. Subjectively, practically all the patients preferred the high-carbohydrate diet. The insulin requirements during the high-fat diets were not quite one-half of that of the other periods but considering the extreme range of the diets, a comparison of the carbohydrate tolerance and insulin coefficient during these periods shows the remarkable flexibility in management allowed by a small difference in insulin. In all dietetic therapy the goal should be as near an approach to the normal diet as is consistent with the underlying pathological conditions. These experiments reveal no reason for imposing markedly abnormal or disproportionate dietary mixtures upon the diabetic patients. They show that the diabetic manifestations of many patients can be equally well controlled on widely varying mixtures. The effort to approach normal diets for such patients would therefore seem logical. If this is so, the dietary objective in the insulin-treated diabetic should be to meet the demands of an individual leading a full normal life. In most instances of uncomplicated diabetics this can be accomplished by a comparatively simple study of the individual needs and desires and the demands of his diabetes. The authors believe that the feeding of insulin-treated diabetic patients does not involve the application of formulae or strict adherence to any particular type of diet. Since these patients do equally well on widely varying diets, the question involved is not one of high fat or high carbohydrate but of a well-balanced, comparatively normal regime.—I. B.

Insulin-refractory diabetes mellitus (Insulinmangelkoma und insulinrefraktäres Koma im Verlaufe eines Diabetes Mellitus). Thannhauser, S. J. and H. Fuld, Klin. Wchnschr. **12**: 252. 1933. Abst., Physiol. Absts. **18**: 352.

Description of a case of diabetes mellitus in which at first the subject responded well to insulin and then a few weeks later became completely refractory and died in coma. Twelve hours before death the blood sugar was 950 mg. per cent, in spite of large doses of insulin. Complete details of the diet and treatment are given. The authors suggest that some factor in addition to insulin is necessary for glycogen synthesis in the liver, and that in the type of case they describe this factor (an enzyme or enzyme-like substance) is missing.

Isolation and demonstration of hormone of parathyroid in blood of pregnant women (Über die Darstellung und den Nachweis des Nebenschilddrüsenhormons im Schwangerenblut). Hoffmann, F., Arch. f. Gynäk. **153**: 181. 1933.

With modification of Collip's method for the extraction of parathyroid hormone from parathyroids, the author succeeded in extracting this hormone from the blood of pregnant women. The extract was tested on dogs and found to contain 2 units in 20-25 cc. of plasma at the end of pregnancy. It first appeared in the blood during the third to fourth month of gestation, and could never be found in non-pregnant women.—H. Selye.

Vagal innervation and parathormone. Taylor, N. B., C. B. Weld and J. F. Sykes, Proc. Am. Physiol. Soc. P. 94. 1933.

The outstanding effects of parathormone overdosage in dogs are hypercalcaemia and intense hyperaemia of the mucosa of the stomach and small intestine, culminating in haemorrhagic extravasation. Rapid post-mortem softening of the gastric wall occurs. The vascular effects upon the gastro-intestinal tract appear to be coextensive with the vagal innervation, going no farther than the lower end of the small intestine. Diarrhea and vomiting, usually haemorrhagic in nature and both referable to vagal activity, are prominent symptoms which supervene a day or two after the commencement of the administration of parathormone. Section of the vagus nerves in dogs though without effect upon the development of hypercalcaemia prevents the appearance of the typical parathormone effects upon the gastro-intestinal mucosa. Atropine also antidotes these effects. None of the animals which received atropine and parathormone had diarrhea or vomited. The animals received maximal doses of parathormone, 4 units per kilo being given every 3 hours throughout the day. One-tenth to 0.2 mg. of atropine per kilo was given with each dose of the hormone. The serum calcium rose abruptly, reaching a height of from 20 to 22 mg. per 100 cc. within 24 hours after the first dose. After death the typical parathormone picture was absent. The intestine was quite pale. No blood was found in the stomach, and the gastric mucosa showed a mild general flushing with a deeper red area in the pyloric antrum. This latter region was alone suggestive of parathormone overdosage. The general appearance of the interior of the stomach was in marked contrast to that seen when an animal was killed by the administration of parathormone without atropine.—Authors' Abst.

The hormone of the spleen. Miwa, T. Tr. Jap. Path. Soc. **21**: 193. 1931. Abst., Chem. Absts. **26**: 6004.

The blood of the splenic vein contains a special hypocalcemic substance which is antagonistic to parathyroid hormone and synergistic with thymic hormone.

On the occurrence of spontaneous glycosuria and alimentary hyperglycaemia in exophthalmic goiter. Andersen, W. T., Acta med. Scandinav. **78**: 229. 1933.

Glycosuria in exophthalmic goiter has often been reported, but the statements as to its frequency are conflicting. In Andersen's studies a special technique has made it possible to demonstrate the presence of spontaneous glycosuria in each of 25 patients with exophthalmic goiter. Twenty-five glucose tolerance tests on 25 patients demonstrated that the alimentary blood sugar curve after ingestion of 70 gm. glucose is higher and more protracted than corresponding curves in healthy individuals.—Author's Abst. (abbreviated).

Clinical and experimental observations upon the heart in hyperthyroidism. Andrus, E. C., Tr. A. Am. Physicians, **47**: 47. 1932.

The cardiac manifestations of hyperthyroidism constitute a prominent phase of this syndrome. Yet it is often difficult, sometimes impossible, to correlate the severity of these with the other clinical signs. Signs of cardiac failure may be so conspicuous as to mask the hyperthyroidism or a patient may perish in thyroid crisis without symptoms of myocardial insufficiency. In the author's series of 200 cases of hyperthyroidism congestive heart failure occurred in 18.5%. The average duration of symptoms was conspicuously greater in the cases with myocardial insufficiency. Its incidence increased in the age decades above 40 years, and was most common in any age group in association with other pre-existing factors which tend to diminish the cardiac reserve such as rheumatic heart disease, hypertension, arteriosclerosis or, more rarely, syphilitic heart disease. It also seems pertinent to call attention to the frequency of auricular fibrillation among the cases with congestive heart failure. A totally irregular ventricular rhythm presents another and a serious handicap to an already overburdened circulation in these instances. In a series of observations it was impossible to demonstrate any direct effect of thyroxine upon the isolated heart in vitro and it is utterly impossible to reproduce Graves' disease in animals by means of repeated injections of thyroxine. It is, however, possible to reproduce the major component of this syndrome, hyperthyroidism. The injection of thyroxine into a rabbit is followed by a series of events which are homologous

with the signs and symptoms of hyperthyroidism in man. During the first 18 to 24 hours no change may be noted. This "latent period" appears to be characteristic of the action of thyroxine. It finds a clinical counterpart in the interval elapsing between the partial removal of the overfunctioning thyroid gland from a patient with Graves' disease and the "post-operative storm" which frequently follows. By the end of 36 hours the animal becomes more than usually responsive to stimuli. Appetite and thirst increase. It may be shown that the basal metabolism rate is augmented. Electrocardiograms taken while the rabbit is at rest and undisturbed reveal that the heart rate is unusually rapid. If the injection is not repeated all these manifestations disappear within the succeeding two weeks. If the administration of thyroxine be continued the animal loses weight, becomes weak and fatigues rapidly upon the slightest exertion, and finally dies in a state of emaciation and exhaustion. A series of observations was made upon certain physiological properties of the heart removed from thyroxinized animals at the height of the thyroxine effect. It was demonstrated that the hearts, or auricles, of such animals continue to beat after isolation, at a rate conspicuously more rapid than those of normal controls. This tachycardia characteristically persists for hours, tending to decrease with time far less than the rate of spontaneous rhythm of the isolated normal heart. This is in contrast with the tachycardia produced by large doses of atropine or adrenaline, which abates rapidly following isolation of the heart. The addition of adrenaline to the bath in which are suspended the auricles from normal and thyroxinized rabbits brings about the same percentage acceleration in both, i.e., a greater absolute acceleration in those of the thyroxinized animal. The auricles from thyroxinized animals are more dependent upon their contemporary oxygen supply than are those of normal controls. By direct volumetric measurements it has been shown that isolated auricles from small guinea pigs to which thyroxine had been administered consumed from 7 to 20% more oxygen per gram of tissue than auricles of similar weight from normal animals. Finally, chemical estimations were made of certain constituents of cardiac and skeletal muscle from normal rabbits and from those which have received thyroxine. The results indicated such a profound displacement of the carbohydrate metabolism of these tissues that their glycogen content was conspicuously depleted for a certain proportion of instances; this is accompanied by an increase in the concentration of lactic acid. These observations suggest that the metabolism of cardiac muscle is augmented as is that of skeletal muscle and of the body tissues generally. The increased circulatory demands created by any conditions which increase metabolism increase conspicuously the work of the heart. In hyperthyroidism the metabolic alterations in the myocardial tissue render this work abnormally expensive. Conceivably these two factors combine in all cases, varying only in duration and degree to bring to the fore the cardiac manifestations of the disease. Their effect may be determined by the soil upon which they are implanted. In individuals whose circulatory reserve has been diminished by age or by organic cardiac disease, they may result in cardiac failure. Presumably this may develop when the load thrown upon the myocardium exceeds or approaches the limits set by its own metabolism.

—I. B.

Therapeutic effect of total ablation of normal thyroid on congestive heart failure and angina pectoris; early results in various types of cardiovascular disease and coincident pathologic states without clinical or pathologic evidence of thyroid toxicity. Blumgart, H. L., J. E. F. Riseman, D. Davis and D. D. Berlin, Arch. Int. Med. **52**: 165. 1933.

The early therapeutic results following total ablation of the thyroid in 10 patients with congestive heart failure or angina pectoris are reported. Attacks of angina pectoris, which were present in two patients before operation, have not recurred since complete thyroidectomy. In one of these patients, before operation the same measured amount of work under standard conditions regularly precipitated attacks. After operation, under the same conditions, as much as six times the same amount of work was performed without attacks of angina pectoris, the exercise being finally terminated because of physical exhaustion. Seven of the nine patients with congestive failure had practically no cardiac reserve after prolonged periods of adequate medical treatment with complete rest in bed, so that the ability to be up and about without symptoms or signs of congestive failure could be attributed confidently to the effects of operation. During the period of observation of three to six months that have elapsed since operation, all of the patients have shown conspicuous improvement. They have

been able to undertake from slight to considerable exertion without the development of palpitation, dyspnea or any signs of congestive failure. The preoperative craving for water has disappeared. The basal metabolic rate of each patient has shown a significant and persistent lowering which has paralleled the most striking improvement. The velocity of blood flow has become slower in seven patients, indicating that the heart is required to do less work under the new post-operative condition than it was able to accomplish when the metabolic rate was normal. These patients may therefore be regarded as being in possession of definite "cardiac reserve." The vital capacity of the lungs showed a decided increase in some patients, though not in all. By means of exercise tests standardized for each of the nine persons with congestive failure, an increased ability to perform light work after operation has been demonstrated. Frequently recurring hemoptysis and pain in the chest have disappeared following operation. One patient who suffered from paroxysmal dyspnea showed improvement for three weeks following operation. On the twenty-second day he suffered from an attack of acute pulmonary edema during which he died. Further experience is necessary to evaluate the possible benefit to be derived from thyroidectomy in this condition, and operation should be undertaken in this type of cardiovascular disease with extreme caution. Following operation patients have had slight dryness of the skin, increased sensitivity to cold, slow growth of hair and a lower heart rate. Thyroid substance has not been given except for short periods to two patients; in the others, it has not been indicated thus far. In one patient with congestive failure who had suffered from continuous attacks of bronchial asthma since childhood, no severe attacks have occurred since operation. The possible beneficial effects of the procedure in other conditions are discussed.—Authors' Summary (abbreviated).

The non-surgical treatment of Graves' disease (Neoperativní léčení nemoci Basedowovy). Charvat, J., Sborník Lékarský, **34**: 1. 1932.

This is a review of the author's experience with 286 cases of Graves' disease at the Clinic of Pelnar in Prague. Since there is still considerable controversy regarding its etiology, the treatment of hyperthyroidism is not yet established on a rational basis. The author observes that with respect to hereditary influences the frequency of cancer in parents of patients was particularly striking, amounting to 20% in this series. Heart disease occurred in 16.4% of the parents. Of 160 patients a history of diabetes in the family occurred in six instances, and in 19 there was elicited a history of liver and gall bladder affections. There was a history of goiter in the families of 17 patients and tuberculosis in 26. In 29% of the cases Graves' disease was preceded by such infections as quinsy, rheumatism, influenza and thyroiditis. The majority of patients ranged between the ages of 20 and 30 years. Only 14% of the total number were men. Since this disease appears to be a constitutional affection, treatment is replete with difficulties and it is just as necessary to treat the individual as the disease itself. In a few cases absolute physical and mental repose led to complete cure. However, rest in a hospital is not always conducive to ideal quietude of body and mind. The author finds luminal, quinine and ergotin serviceable especially if these are used in combination. Quinidine, in the absence of specific heart indication, is of very limited use. The author has had very little result from the use of opotherapy. However, opolumin (a Czech remedy) composed of hypophysis, pancreas and thymus, one gram of fresh gland of each, combined with 0.01 grain of luminal and 0.04 gram of quinine hydrobromide per tablet in doses of 1 to 3 tabloids one to 3 times daily is advocated. Insulin was tried systematically on 30 patients in doses of 10 units daily, ½ hour before lunch. In five cases this resulted in absolute failure and even damage to the patient; there was slight success in 17 cases and striking effect up to complete cure in 8 cases. Insulin is of use as a fattening remedy but should not be administered to cachectic patients whose livers are poor in glycogen. In the author's experience with iodine medication he found in 18 patients, who were treated by other physicians before entering the hospital, 6 who presented iodine Basedow from simple goiter, in 9 cases the hyperthyroidism was aggravated, in one case there was no improvement, while in two some improvement was observed. The author treated 29 ward patients and 20 outpatients with iodine in small doses. Of these there was no effect in 7 cases, the symptoms were aggravated in 16 and improved in 26. Generally, results were better in patients under observation at the hospital. While in general the primary iodine improvement was followed after a certain time by aggravation

of symptoms, some patients were completely cured after prolonged treatment. The author found that with combined treatment, i.e., iodine in combination with quinine hydrobromide, luminal and ergotin (under the trade name of hypothyrin) there was improvement in all cases and complete cure in some. In cases complicated by rheumatism large doses of sodium salicylate proved effective. X-ray treatment was found useful in early cases of hyperthyroidism but is contraindicated in severe cases. Climatic treatment is of some use. While a sea climate is generally contraindicated in these patients they do well at moderate elevations. The diet advocated is that of non-irritating food poor in proteins, rich in carbohydrates and vitamins. Tea, coffee and tobacco are prohibited. Digitalis and strophanthus are not to be employed in the tachycardia of Graves' disease but sedatives are indicated. In concluding, the author states that by internal treatment he has achieved more or less success in 77% of his cases (a complete cure in only 10%, the mortality rate being a little over 5%). The problem is not what method is most justified, but rather in what cases combined treatment should be used. The patient should not be sent to the surgeon unless prolonged internal treatment has been found lacking. Theoretically, Graves' disease is in the domain of the internist since it is a constitutional syndrome. In toxic adenoma surgery is indicated after a preliminary period of medical preparation. From a practical viewpoint the task of the management of hyperthyroidism is the combined responsibility of internist, roentgenologist, and surgeon, since no one of them is self-sufficient.—I. B.

Iodine metabolism of normal and thyroidectomized goats after potassium iodide and plant iodide feeding (Untersuchungen über den Jodstoffwechsel normaler und thyroidektomierter Ziegen bei Jodkali—und Pflanzenjodfutterung). Courth, H., Biochem. Ztschr. **238**: 162. 1931.

Goats were fed daily the following ration: 1 kgm. chopped hay, 150 grams oats, 150 grams barley, 250 grams potato flakes and 100 grams crushed soy beans. The animals during the iodine period received either 10 mgm. iodine as potassium iodide or an equivalent of plant iodine in radish leaves. A three-day preliminary period, four-day iodine period and an eight-day after period was the custom during the investigative period. The urine and feces were collected twice daily. The goats were milked twice daily. Iodine determinations were made on milk, urine and feces. With a normal goat receiving 10 mgm. iodine for four days the iodine content of the milk rose from .008 mgm. in the preliminary period to 6.029 mgm. on the last day of the iodine period. In the after period the iodine content of the milk gradually decreased from 2.143 mgm. to .098 mgm. on the last day. Of the total iodine eliminated 21.265 mgm. was in the milk, 9.637 mgm. in the urine and 1.095 mgm. in the feces. With the thyroidectomized goat slightly more iodine, 25.334 mgm. was eliminated in the milk, 10.300 mgm. in the urine and only .549 mgm. in the feces. When plant iodide, 9.933 mgm. for four days, in the form of radish leaves, was fed, 15.541 mgm. was eliminated in the milk, 16.939 mgm. in the urine and .399 mgm. in the feces. With a thyroidectomized goat receiving the same amounts of plant iodide (9.933 mgm.) in radish leaves, the iodine content of the milk was 18.674 mgm. the urine 16.691 mgm. and the feces .825 mgm. The amount of milk was increased by both the potassium iodide and plant iodide.—E. L.

The effect of feeding desiccated thyroid upon the sexual maturation of the albino rat. Da Costa, Esther and A. J. Carlson, Am. J. Physiol. **104**: 247. 1933.

Sixty female albino rats fed 0.5 to 1 mg. of desiccated thyroid daily showed a slight acceleration (approx. 215 days) in sexual maturation, while 41 fed 5 to 10 mg. of thyroid daily showed a retardation in pubescence (approx. 15 days). In several groups of male albino rats (3-9 animals each) fed 0.5 to 10 mg. of desiccated thyroid daily a decidedly lower relative weight of the testes than in the controls was the rule. This relationship was seen even when the body weight of the thyroid-fed rats was greater than that of the controls. In most cases the sexual maturation of the gonads of the male rat was depressed by thyroid feeding (0.5-10 mg. per day).

—Correction of abstract previously published—**18**: 308. 1934.

The effect of thyroxine and of iodine in a dosage analogous to the iodin content of thyroxin on some phases of metabolism on the blood, etc., in endemic cretins (Uber die Wirkung des Thyroxins und des Jodes in einer dem Jodgehalt des Thyroxins entsprechenden Dosierung auf einige Abschnitte des Stoffwechsels, auf das Blut usu. bei endemischen Kretinen). Fonio, A. and G. Scheurer, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **42**: 467. 1931.

The following observations were made on eight cases of endemic cretins: basal metabolic rate, coagulation time, hemoglobin, blood pressure, body weight and specific gravity of the urine. By medication with thyroxine the basal metabolism was increased, the coagulation time increased, the hemoglobin increased, the blood pressure slightly decreased and the body weight usually decreased. Similar results were produced by iodin in analogous doses to the iodin content of thyroxine. The effects of iodin medication were usually slightly less.
—E. L.

Total and thyroxine iodine content of thyroid gland after injection of saline anterior pituitary extracts. Foster, G. L., A. B. Gutman and E. B. Gutman, Proc. Soc. Exper. Biol. & Med. **30**: 1028. 1933.

After 10 daily intraperitoneal injections of a saline anterior pituitary extract, there was a decrease in the total iodine content of the thyroid glands of five sheep, with a proportionate decrease in the thyroxine content.—M. O. L.

Rôle of diiodotyrosine in hyperthyroidism: comparison of therapeutic effect of diiodotyrosin with inorganic iodine. Gutman, A. B., L. W. Sloan, Ethel B. Gutman and W. W. Palmer, J. A. M. A. **101**: 256. 1933. Abst., A. M. A.

The authors prepared 30 patient with hyperthyroidism for thyroidectomy by administering diiodotyrosine. They were more impressed with the similarities than by the differences between the response of hyperthyroid patients to diiodotyrosine and to other iodine compounds. The effects are indistinguishable as to time of onset of remission, the period required for maximum response, the duration of remission, the exacerbation when medication is discontinued, the response when again administered, the ultimate development of a refractory state, the success of intermittent dosage in mild cases, and the characteristic clinical, metabolic, histologic and chemical changes common to the two. The conclusion that the effects of diiodotyrosine and of inorganic iodine are essentially the same appears justified. It has been suggested by Abelin that the effects of iodine in hyperthyroidism are due to the influence of diiodotyrosine that is formed. Ignorance of the intermediary iodine metabolism of the thyroid makes it impossible to prove or disprove this assumption. Diiodotyrosine has not been conclusively shown to have any physiologic activity that could be regarded as antagonistic to thyroxine. The lowering of the basal metabolic rate of animals fed thyroid by added diiodotyrosine was not observed by Kommerell in dogs or in the authors' laboratory in guinea-pigs. Diiodotyrosine does not lower the basal metabolism of normal animals, as might be expected of a substance having an effect antagonistic to thyroxine. One might expect, furthermore, that administration of thyroxine in the form of thyroid gland, which also contains a large proportion of diiodotyrosine, would not produce as great an effect on the metabolism as an equivalent amount of thyroxine in the form of the free amino-acid. That this is not the case is well established. The authors point out that the only definite physiologic activity that diiodotyrosine has been shown to possess is the acceleration of metamorphosis in amphibia, in which respect it acts like thyroxine.

Thyroid gland deficiency in chronic arthritis. Hall, F. C. and R. T. Monroe, J. Lab. & Clin. Med. **18**: 439. 1933.

Three hundred cases of chronic non-tubercular arthritis were reviewed for the signs and symptoms of thyroid deficiency, the basal metabolic rates, the action of thyroid gland therapy, and the results of medical treatment, which included thyroid substance. Of these, 150 were of the atrophic type of arthritis and 150 were of the hypertrophic type. In the hypertrophic group of cases the symptoms and signs of hypothyroidism occurred with great frequency, with no other obvious explanation for them. The basal metabolic rates were below minus 10 in 50%, and below minus 15 in 34.2% of 100 cases, even though most

of them were determined under inadequate conditions of rest and in the presence of pain. In 42 cases no basal metabolic rate determinations were made. They were for the most part well nourished individuals and no other explanation for the hypometabolism was apparent except the glandular deficiency. Thyroid gland therapy was of permanent beneficial effect in 49.1% of 116 cases in whom it seemed wise to use it. In the atrophic group of cases the signs and symptoms of hypothyroidism were less frequent and generally could be accounted for on the basis of depletion and undernutrition. The basal metabolic rates were below minus 10 in 35.6% and below minus 15 in 17.7% of 106 cases. No basal metabolic rate determinations were made in 44 cases. Definite glandular deficiency seemed present in only a small number, and there was usually another explanation for the hypometabolism. Thyroid gland therapy was of permanent beneficial effect in 16.5% of 103 patients in whom it seemed wise to use it. Thyroid deficiency appears to be a contributing etiologic factor in certain patients with chronic arthritis, as well as infection, dietary deficiency, trauma, and depletion. Its correction improves the general well-being of the patient, aids in relief of joint pain and disability, and helps to lay a foundation for permanent control of the arthritis, probably through better joint nutrition.
—I. B.

Lymphoma of the thyroid; report of two cases. Lerman, J., M. Clin. North America, **16**: 1003. 1933.

The two cases presented illustrate an important type of thyroid disease, usually wrongly diagnosed as carcinoma. We must bear in mind that it is entirely possible for the thyroid to give rise to lymphoma, alone or in conjunction with other organs, because this process may develop in any organ where lymphoid tissue is present. In actual experience, however, we rarely see lymphoma of the thyroid and the number of reported cases is small. This is surprising since in exophthalmic goiter focal or diffuse lymphoid infiltration is a feature. The first of the cases reported is particularly interesting because the thyroid only was involved; there is no evidence at present to indicate that any other part of his body is the seat of lymphomatous change. In the second case the thyroid was the first organ to be involved, followed six years later by involvement of the cervical glands and a year after this by enlargement of the spleen. In both instances a diagnosis of carcinoma of the thyroid was made on clinical grounds. From the experience with these patients the author believes that it is of the utmost importance to consider lymphoma in the differential diagnosis of carcinoma of the thyroid since the response to radiation and the chance of prolonging life are very much better in the former than in the latter. The diagnosis must be settled by examination of a biopsy specimen, although the rapid disappearance of the tumor with radiation should suggest it. The treatment of lymphoma of the thyroid as demonstrated by these two cases is radiation. It causes rapid disappearance of the tumor and alleviation of pressure symptoms. In case 1 the mass in the thyroid was entirely absent at the end of nine months. At present, after four years, there is no evidence of recurrence. It is not at all unlikely that this represents one of the rare cases with a single lesion, treated before the disease became generalized. The remarkable disappearance of the thyroid tumor in the neck and in the mediastinum in case 2 was dramatic. Although the disease probably has been present for ten years, it has been held in check by radiation for the past 4½ years. A similar patient reported by Krammer lived for 12 years after surgical removal of part of the thyroid tumor followed by radiation. It follows that in venturing a prognosis in this type of thyroid lesion we must not be too pessimistic. There is the possibility of complete cure if treated when the disease is still localized, or, at least, the condition may be kept in check for many years.—I. B.

Effect of sunlight and darkness on the thyroid gland. McCarrison, R., Indian J. M. Research, **20**: 633. 1933. Abst., Physiol. Absts. **18**: 359.

An experiment has been carried out with rats to test the view that lack of light may contribute to the causation of goiter. It was found that darkness did not exert any action which was favorable to goiter production. On the other hand, there was an increased tendency of goiter production in those animals which were exposed to sunlight. The basal diet of the animals was markedly deficient in vitamins A and C and was favorable to goiter-production

The effect of insanitary condition on the thyroid gland and other organs of the body. McCarrison, R. and K. B. Madhava, Indian J. M. Research, **20**: 637. 1932. Abst., Physiol. Absts. **18**: 359.

The goitrogenic potency of cabbage varies with season and seems to be related in some way to rainfall, being at its maximum during and after the heavy autumn rains. When albino rats were kept on a diet of cabbage, whole wheat, and cholam (Andropagam sorghum)—which was not in itself goitrogenic—they became goitrous when living under conditions of gross insanitation, but remained goiter-free when living under conditions of scrupulous cleanliness. In association with insanitary condition, the existence of a "goiter noxa" of unknown nature has also been demonstrated. The effect of insanitary condition is not limited to the enlargement of the thyroid gland. Associated with the hypertrophy of this organ there is an increase in size of the adrenal glands and spleen, and a reduction in size of testicles and thymus.

The relation of maternal metabolism to infant birth weight. Mengert, W. F., Surg., Gynec. & Obst. **56**: 1009. 1933.

Englebach has supported the thesis that the birth weight of infants is materially influenced by the level of thyroid function in the mother. Corresponding endocrine interest attaches to Mengert's correlation study of the basal metabolic rates of 203 mothers and the weights of their offspring. An instructive scatter graph is published that shows clearly a random distribution of birth weights through a range of maternal rates from—18 to + 40.—R. G. H.

Lingual goiter. Miller, R. H., New England J. Med. **208**: 480. 1933.

Report of a case of the permanent localization of the entire thyroid gland at the base of the tongue.—J. C. D.

The use of continuous venoclysis of glucose after thyroid operations. North, J. P., Pennsylvania M. J. **36**: 495. 1933.

Postoperative thyroid crises constitute a serious and frequently fatal complication after thyroidectomy. Although the exact nature of these crises is obscure, there is evidence that glucose depletion and dehydration exist during the critical period. For some time we have attempted to satisfy these requirements by giving 5% glucose in physiologic saline by venoclysis. The uniformly mild grade of postoperative reaction in a group of 100 severely toxic thyroid patients appeared to justify this procedure.—I. B.

Hypophysectomy and thyroidectomy of snakes. Schaefer, W. H., Proc. Soc. Exper. Biol. & Med. **30**: 1363. 1933.

Removal of the hypophysis in garter snakes invariably caused shedding of the skin, usually repeated. Two thyroidectomized snakes also shed the skin 5 and 6 times. The feeding of thyroid both to thyroidectomized and hypophysectomized snakes prevented shedding.—M. O. L.

Action of fluorine on histological aspect of thyroid (Influencia del tratamiento fluórico sobre la estructura histológica de la tiroides). Schteingart, M. and R. Sammartino, Rev. Soc. argent. de biol. **8**: 505. 1932.

A patient with Basedow's disease was treated with intravenous injections of fluorine, 1 cc. (25% solution) every 2 or 3 days for 6 months. The basal metabolism before treatment was +48%. During treatment it was always above +50% and as high as +71%. After thyroidectomy it was +10%. Histological preparations showed a state of activity of tissue. Sclerosis was not observed. Fluorine treatment had no favorable results.—J. T. L.

Chronic invalidism with marked personality changes due to myxedema. Stoll, H. F., Ann. Int. Med. **6**: 806. 1932.

Six case reports demonstrate the marked personality changes present in the advanced cases. The main symptoms are: irritability, untruthfulness, suspicion, delusions, retarded cerebration, inability to concentrate, introversion, and failing memory. Accompanying clinical symptoms were: Anemia, marked

elevation in blood cholesterol, myxedema heart, lack of perspiration, bleeding hemorrhoids. The frequent failure to recognize the condition is particularly deplorable because the transformation of the old and feeble-minded caricature of humanity into an alert, normal person by the administration of thyroid is one of the triumphs of medicine.—G. L. Banay.

Acute suppurative thyroiditis with report of one case. Weinstein, M. L., Illinois M. J. **63**: 275. 1933.

This article consists of a review of the literature, etiology and treatment of suppurative thyroiditis, with report of a case. The patient was a three-year-old child with a history of abnormal behavior for three days and swelling and pain in the neck for one day, fever, chills, and discomfort. Incision and drainage were resorted to and the child was able to leave the hospital within two days, entirely recovered. Cases of thyroiditis must be followed up for signs of hypothyroidism.—I. B.

Glucose metabolism in hyperthyroidism (El metabolismo de la glucosa en el hipertiroidismo). Yriart, M. and H. Gotta, Rev. Soc. argent. de biol. **8**: 604. 1932.

The specific dynamic action of glucose was determined in 15 cases of hyperthyroidism. Respiratory metabolism was determined before and every 30 min. up to 2½ hours after the ingestion of 1.75 g. glucose per kg. and the blood sugar was followed up to 3 hours after. The same observations were made in 10 of these patients after their thyroid had been extirpated. The average basal R.Q. was 0.74 before and 0.785 after operation. After ingestion of glucose the R.Q. rose to 1 or above (in 5 cases), the average maximum being 0.97 before operation. After thyroidectomy the maximum R.Q. observed was 0.85-0.93 (average 0.90). Fasting blood sugar was slightly higher during hyperthyroidism, average values being 113 mg. per cent before and 104 mg. per cent after operation. The rise after ingestion of glucose was steeper, reached a higher level and the blood sugar remained above the initial figure for a longer period before than after the operation. Hyperthyroidism does not diminish the capacity to burn glucose, but enhances it. A prolonged hyperglycemia after glucose injection cannot be considered as exclusively due to deficient utilization of glucose.—J. T. L.

Blood constituents in Basedow's disease (Zur Klinik des M. Basedow unter besonderer Berucksichtigung des Blutbildes). Zimmerman, O., Wien. klin. Wchnschr. **46**: 265. 1932.

Observations were made on the blood changes in 100 patients with hyperthyroidism. Twenty-seven per cent of the patients had erythrocyte counts over 5.0 million per cc. and 7% under 4.0 million. The hemoglobin content and color index were within normal limits. Abnormal degrees of poikilocytosis, anisocytosis, polychromatophilia and neucleation of red cells were not found. The platelets varied within the normal values of about 200,000 to 400,000. The only evidence for an endocrine influence on the erythropoietic activity of the bone marrow was an increase in reticulocytes. In 60% of the patients the reticulocyte values were 5% or more. The leucocytes varied from 2,700 to 12,500 per cc. Twenty-three per cent of the patients showed values over 7,000 cells and 33% under 5,000 cells. A relative lymphocytosis (over 30%) was present in 60% of the patients but in the two-thirds this was due to the neutropenia. The monocytes were slightly increased, the eosinophiles normal, and basophiles diminished. In 40% of the patients the clotting time was greater than normal, without relationship to the severity of the disease. In 80% of the patients the sedimentation rate was faster than normal. The rate of sedimentation tended to parallel the severity of the disease. A positive Rumpel-Leede sign was present in 75% of the patients tested. The degree of reaction conformed to the severity of the disease. Any one of these findings is of little significance, but the combination of neutropenia, relative lymphocytosis, increased number of reticulocytes, rapid sedimentation rate and a strongly positive Rumpel-Leede sign is of value in diagnosis and prognosis when interpreted in conjunction with electrocardiographic findings and basal metabolic rate.

—J. Lerman.